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A mathematical algorithm that computes breast cancer sizes and doubling times detected by screening

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Abstract

This paper presents a mathematical algorithm that computes the sizes and growth rates of breast cancer detected in a hypothetical population that is screened for the disease. The algorithm works by simulating the outcomes of the hypothetical population twice, first without screening and then with screening. The simulation without screening relies on an underlying model of the natural history of the disease. The simulation with screening uses this natural history model to track the growth of breast tumors backwards in the time starting from the time they would have been detected without screening. The method of tracking tumor growth backward in time is different from methods that track tumor growth forward in time by starting from an estimated time of tumor onset. The screening algorithm combines the natural history model, the method tracking of tumor growth backward in time, the age group, the interval between screening exams, and the detection threshold of the screening exam to compute the joint distribution of tumor size and growth rate among screen-detected and interval patients. The algorithm also computes the sensitivity and leadtime distribution. It allows for arbitrary age groups, detection thresholds and screening intervals and may contribute to the design of future screening trials. © 2001 Published by Elsevier Science Inc.

Keywords: Breast cancer screening; Tumor size; Tumor growth rate; Mathematical model; Simulation

1. Introduction

Breast cancer is a leading cause of death among women in the United States [1]. The purpose of screening for the early detection of breast cancer is to reduce breast cancer mortality. Current screening guidelines are based on prior randomized controlled trials that demonstrated a reduction in breast cancer mortality from screening with conventional mammography. Yet new breast

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cancer imaging technologies are emerging that may more accurately detect breast cancer than conventional mammography. These new technologies have generated interest in altering the current guidelines. However, measuring breast cancer mortality reduction for every possible new screening guideline with a traditional randomized controlled trial (RCT) is not feasible. RCTs demand large resources, long follow-up periods and high patient compliance. The screening technology is also likely to be updated or outdated before the trial is over. Consequently, the rapid development of promising new screening technologies is posing a new challenge in technology assessment and the formation of new screening guidelines.

This manuscript presents a mathematical algorithm that simulates breast cancer screening in a hypothetical population in order to help design and analyze screening trials as well as analyze population-based breast cancer surveillance data. The model can simulate screening programs under a variety of conditions. It allows for variations in the interval between screening examinations, the probability that the screening exam can detect a tumor of a given size, and the age group that is screened. It computes the sensitivity of the screening exam for the first and subsequent screening rounds. It computes the leadtime distribution per screening round and the leadtime distribution conditioned on the tumor growth rate. Finally, the algorithm computes the joint distribution of tumor size and growth rate of breast cancer among screen detected and interval patients. Interval patients refer to screened patients who become clinically detected with breast cancer during the interval between consecutive screening examinations.

This manuscript focuses on the intermediate outcomes of breast cancer screening, in particular the detected tumor size and tumor growth rate. The intent here is to emphasize that analyzing the effect of screening on tumor size alone is not sufficient. Oftentimes, it is assumed that if a screened population has a larger fraction of small tumors compared to a non-screened population, the screened population would have lower breast cancer mortality. However, experience has shown that a shift to smaller tumors does not necessarily translate into a health benefit. Screening may be detecting slower growing tumors, while missing faster growing tumors, yet faster growing tumors are likely to be more aggressive that slower growing tumors. Simulating the tumor growth rate as an output of the screening model can provide a proxy to the biological behavior of the tumor. With such a screening simulation model, we may gain insight into tumor growth rates that could be detected by screening under a wide range of values for the screened age groups, screening intervals and probability that the screening exam can detect a tumor of a given size. Such an analysis would not be feasible nor ethical with clinical trials.

2. Background

For more than three decades, mathematical models have been proposed to analyze and predict the outcomes of breast cancer screening programs. The first group of models was developed before most major RCTs in breast cancer screening had accrued long enough follow-up data to show a statistically significant mortality reduction from screening. These early models relied on various assumptions about the natural history of the disease, such as the tumor growth rate, the probability of detecting a tumor of a given size, survival given the size of the tumor at detection, and the rate of clinical surfacing [2,3].

Once major randomized controlled trials had accrued long enough follow-up data, an alternative group of screening models emerged. These methods extended the health benefit measured

by the RCTs to larger populations in order to predict the impact of screening on national breast cancer trends. They analyze the effect of alternative start and stop ages of screening and incorporate costs that were not collected by the screening trails [4]. Data from the RCTs have also been used to infer the leadtime of screening [5], which is then incorporated into simulation-based algorithms of screening [6,7]. In general, these models are bound to the protocol analyzed by the RCTs (i.e. age-groups, screening interval, screening exam) and have not been extended to predict the outcomes of screening protocols that were not tested by RCTs.

When the controversy over screening women ages 40–49 years arose, it was argued that existing RCT data were not sufficient to reach a consensus. Screening models based on the natural history of the disease were revisited to better understand the effect of screening on breast cancer mortality reduction [8–11]. For example, Jansen et al. [8] proposed a simulation-based analysis based on assumptions of tumor growth rate, the probability of detecting a tumor of a given size, 10-year survival given the size of the tumor at detection, and the rate of clinical surfacing. Michaelson et al. [11] proposed a natural history model to quantify the reduction in patients with metastatic disease from screening. These models are intended to simulate screening under a variety of age groups, screening intervals and detection thresholds. Detection threshold of the screening exam refers to the tumor size at and above which can be screen detected and below which cannot be screen detected.

This manuscript presents a mathematical model of breast cancer screening based on assumptions of the natural history of the disease. Similar to the previous natural history screening models, this model can simulate screening programs under a variety of age groups, detection thresholds, and screening intervals. However, this model is different from the previous ones in four key ways. First, this model does not estimate the size of the tumor at onset and then track the tumor growth forward in time until the tumor is detected. It instead tracks the tumor growth backwards in time. It uses information above the tumor size when it is clinically detected in a non-screened population and searches backwards in time to determine the earliest moment the tumor may have been screen detected. Hence, it relies on the tumor growth around the time of clinical detection, which is observable, as opposed to tumor onset, which is not observable. Second, this model allows the possibility that the detected tumor size and growth rate may be correlated. It is analytically derived based on assumptions of the joint distribution of the tumor growth and tumor size in a non-screened population. Third, this model provides the leadtime distribution, as well as the leadtime distribution conditioned on the growth rate. Finally, it provides both the transient and steady-state effects of screening.

3. Methods

This section describes the screening algorithm. The algorithm simulates the effect of screening by tracking the breast tumor growth backwards in time, starting from the time the tumor would have been clinically detected without screening. It computes tumor sizes and growth rates for the screen-detected and interval patients. Breast tumors are assumed to be spherical and tumor size refers to the tumor's diameter. Breast tumors are assumed to grow exponentially. Tumor growth rate is described by tumor volume doubling time, and abbreviated as doubling time. Doubling time is the product of the inverse of tumor growth rate and $\ln(2)$.

3.1. Screening algorithm

The screening algorithm is composed of two state-transition models. The first state-transition model tracks a hypothetical cohort of women without screening over a period of K years. It determines the annual breast cancer incidence and the annual joint distribution of tumor size and doubling time. The second state-transition model tracks the same hypothetical cohort and retraces the same K-year period observed in the first model, but imposes a breast cancer screening program at the start of the K-year period. It uses the outcomes of the first model along with the screening schedule and detection threshold of the screening exam to determine the sensitivity of screening, the joint distribution of tumor size and doubling time among screen detected and interval patients, and the leadtime distribution of screening.

3.1.1. Modeling the cohort without screening

The state-transition model that analyzes the hypothetical cohort without screening is shown in Fig. 1. The state are 'well' for women who are alive and asymptomatic of breast cancer, 'clinically detected' for women who are clinically detected with breast when clinical symptoms appear such as pain and swelling, 'death from other causes' for women who have been asymptomatic and die from causes other than breast cancer. Transitions between the states occur annually. Time is indexed as year k, where $k = \{0, 1, \ldots, K\}$. The 'clinically detected' state at year k is represented by $C(k)$; the 'death from other causes' state at year k is represented by $X(k)$; and the 'well' state at year k is represented by $W(k)$. At year 0, the entire cohort is in the 'well' state. As time progresses, women can remain in 'well' or enter 'clinically detected' or 'death from other cases'. Year K is defined as the first year in which no women are in the 'well' state.

3.1.1.1. State-transition probabilities. Three state-transition probabilities are associated with Fig. 1. The first, represented by $\lambda_C(k)$, is the transition probability from $W(k-1)$ to $C(k)$. The second, represented by $\lambda_X(k)$, is the transition probability from $W(k-1)$ to $X(k)$. The third, represented by $\lambda_W(k)$, is the transition probability from $W(k-1)$ to $W(k)$. The transition probabilities can be obtained from epidemiological data. Since $\lambda_C(k)$ is equivalent to breast cancer incidence at year k in non-screened cohort, it can be obtained from epidemiological studies prior to a time screening is offered. The transition probability $\lambda_X(k)$ can be obtained from life-table data that are adjusted to remove the probability of death from breast cancer before being diagnosed with breast cancer.

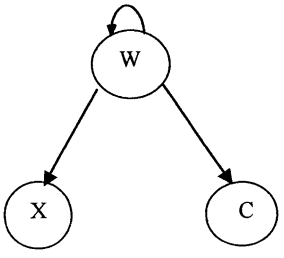

Fig. 1. The state-transition model for the non-screened cohort, illustrating the states 'well' (W), 'clinically detected with breast cancer' (C) and 'death from other causes' (X).

The probability that a woman returns to the well state is computed as $\lambda_W(k) = 1 - \lambda_D(k) - \lambda_X(k)$. The transition probabilities can be age-specific.

3.1.1.2. Number of patients in the health states. The number of women in the states 'well', 'clinically detected' and 'death from other causes' at year k is represented by $N_W(k)$, $N_C(k)$, and $N_X(k)$, respectively. At year 0, the size of the cohort is N_0 and entire cohort is in the well state, hence $N_W(0) = N_0$, $N_C(0) = 0$, and $N_X(0) = 0$. Given the state-transition probabilities at year k, the number of women in each state can be computed as follows:

$$\begin{aligned} N_C(k) &= \lambda_C(k)N_W(k-1), \\ N_W(k) &= \lambda_W(k)N_W(k-1), \\ N_X(k) &= \lambda_X(k)N_W(k-1). \end{aligned} \tag{1}$$

3.1.1.3. Approximating the joint distribution of tumor size and doubling time. The joint distribution of tumor size and doubling time in $C(k)$ is represented by $\chi(s, \alpha \mid C(k))$, where s represents the tumor diameter and α represents the tumor volume doubling time. Using Bayes theorem, it can be expressed as

$$\chi(s, \alpha \mid C(k)) = f(s \mid C(k), \alpha)\varphi(\alpha \mid C(k)), \tag{2}$$

where $f(s \mid C(k), \alpha)$ represents the tumor size distribution among the women in $C(k)$ whose doubling time is α; and $\varphi(\alpha \mid C(k))$ represents the distribution of the doubling time among the women in $C(k)$.

Since $\chi(s, \alpha \mid C(k))$, $f(s \mid C(k), \alpha)$, and $\varphi(\alpha \mid C(k))$ cannot be observed, they are approximated. It is often assumed that the detected tumor size and doubling time are independent, allowing the joint distribution to be expressed as

$$\chi(s, \alpha \mid C(k)) = f(s \mid C(k))\varphi(\alpha \mid C(k)). \tag{3}$$

The size distribution $f(s \mid C(k))$ can be obtained from epidemiological data prior to the start of screening, but the doubling time distribution $\varphi(\alpha \mid C(k))$ cannot be observed in an ethical manner. The doubling time has been observed with retrospective data where a tumor happens to appear on serial screening mammograms, but these measurements bias the doubling time distribution toward the slower growing tumors [12–15]. Limited studies also exist where multiple serial mammographic measurements were found prior to surgery for patients who were not necessarily screen detected [16].

In the early 1980s, a mathematical model of the joint distribution of tumor size and growth rate proposed a correlation between the detected tumor size and the doubling time. Atkinson et al. [17] constructed a mathematical theory of tumor growth and detection predicated on three hypotheses. The first hypothesis states that if a tumor has not been detected by time t, then the probability that it becomes detected in the interval $[t, t + \Delta t]$ is

$$bv(t)\Delta t + \mathrm{o}(\Delta t), \tag{4}$$

where b is a constant and $v(t)$ is the tumor volume at time t. Therefore, a larger tumor is more likely to be detected than a smaller tumor. This hypothesis may be best suited for a non-screened

population where the detected tumor size is not affected by the constraints imposed by the screening test. Atkinson et al. proceeded with the second hypothesis that the tumor volume grows exponentially with doubling time α

$$v(t) = c \exp\left[\frac{t \ln(2)}{\alpha}\right], \tag{5}$$

where c is the volume of a single tumor cell. Combining these hypotheses, they derive the following expression for the distribution of the detected tumor volume conditioned on the doubling time α

$$f(v|\alpha) = \frac{\alpha b}{\ln(2)} \exp\left[-\frac{\alpha b(v-c)}{\ln(2)}\right]. \tag{6}$$

The derivation and validation of Eq. (6) can be found in [17], but conditioned on the inverse of the growth rate instead of the doubling time. Eq. (6) indicates that a small tumor at clinical detection is likely to have a slower doubling time, and a large tumor at clinical detection is likely to have a faster doubling time. For a spherical tumor with diameter s, the volume is $v = (4/3)\pi(s/2)^3$, and Eq. (5) can be re-expressed as

$$f(s|\alpha) = \frac{1}{2\ln(2)} \alpha b \pi s^2 \exp\left[-\frac{\alpha b}{\ln(2)}\left(\frac{\pi}{6}s^3 - c\right)\right] \tag{7}$$

by applying a change of random variables to the probability distribution, $f(v|\alpha)$ [18].

Atkinson et al. added the third hypothesis that $\underline{\alpha}$, which is defined here as $\alpha/\ln(2)$, has the gamma distribution

$$\phi(\underline{\alpha}) = \frac{a^r}{\Gamma(r)} \underline{\alpha}^{r-1} \exp[-\underline{\alpha} a], \tag{8}$$

where r and a are the shape and scaling parameters. In terms of the doubling time α, Eq. (8) can be re-expressed as

$$\phi(\alpha) = \frac{a^r}{\ln(2)\Gamma(r)} \left(\frac{\alpha}{\ln(2)}\right)^{r-1} \exp\left[-\frac{\alpha a}{\ln(2)}\right]. \tag{9}$$

Eqs. (7) and (9) are fully determined once the parameters a, b and r are estimated. Atkinson et al. [17] provided varying estimates for a, r and b using data from about 4000 breast cancer patients seen in the MD Anderson Center between the years 1945 and 1981.

In Section 4 (Results), these equations will be used as the input for deriving the joint distribution of tumor size and doubling time of the non-screened cohort.

3.1.2. Modeling the cohort with screening

The state-transition model that analyzes the hypothetical cohort with screening is shown in Fig. 2. There are K groups of states, where each group consists of the following three states: (1) a 'preclinical' state for women who are asymptomatic for breast cancer, (2) a 'screen detected' state for women who are screen detected with breast cancer, and (3) an 'interval' state for women who are clinically detected with breast cancer between screening examinations. This model follows the same hypothetical cohort that was previously followed without screening. Time is reset to year 0 and the period from year 0 to year K is re-analyzed. At year 0, the subset of women who were

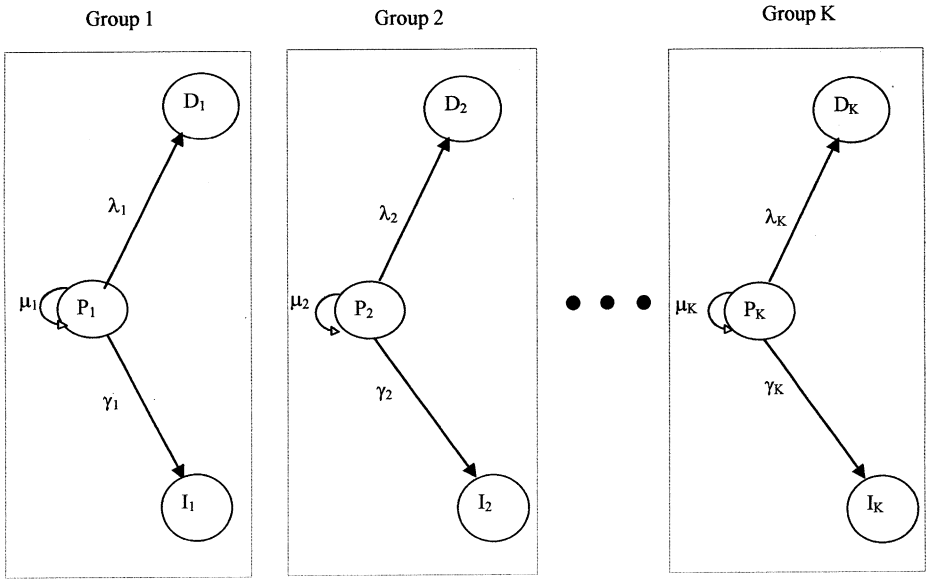

Fig. 2. The state-transition model for the screened cohort. Only the subset of women who were clinically detected with breast cancer in the non-screened cohort model is tracked in the screened cohort model. There are K groups of states, where each group has three states: 'preclinical' (P), 'screen detected' (D) and 'interval detected' (I). K is the number of years needed for all the women to exit the well state in the non-screened cohort model. (In the text, interval patients are referred to as clinically detected patients after screening stops.)

detected with breast cancer from the non-screened cohort is identified. These women are assigned to one of the K preclinical states, where the jth preclinical state at end of year k is represented by $P_j(k)$. At year 0, women are assigned to $P_j(0)$ if they would have been clinically detected with breast cancer by the end of year j had they not been screened. As time progresses, women in a preclinical state can either remain in that state, become detected with breast at the time of screening, or become clinically detected in the interval between screening examinations. $D_j(k)$ represents the jth screen detected state by the end of year k. $I_j(k)$ represents the jth interval state at the end of year k. This state-transition model does not allow the possibility of women to transition from a preclinical state to death. It has already been established that these women do not die before becoming diagnosed with breast cancer, else they would have done so in the previous state-transition model that followed the same cohort without screening.

A six-step algorithm dynamically determines the annual transition probabilities, the annual incidence in each state and the annual joint distribution of tumor sizes and doubling times in each state. Step 1 occurs at year 0 and initializes the incidence and the joint distribution of tumor size and doubling time in each state. Steps 2–5 occur at year k for $k = \{1, \ldots, K\}$. Step 2 computes the state-transition probabilities at year k. Step 3 computes the breast cancer incidence in each state at year k. Step 4 computes the joint distribution of tumor size and doubling time among the screen detected patients in year k. Step 5 computes the joint distribution of tumor size and doubling time among the interval patients in year k. Step 6 computes the joint distribution of tumor size and doubling time among the preclinical patients in year k. The six-step algorithm is illustrated in Fig. 3 and described in detail in the following section.

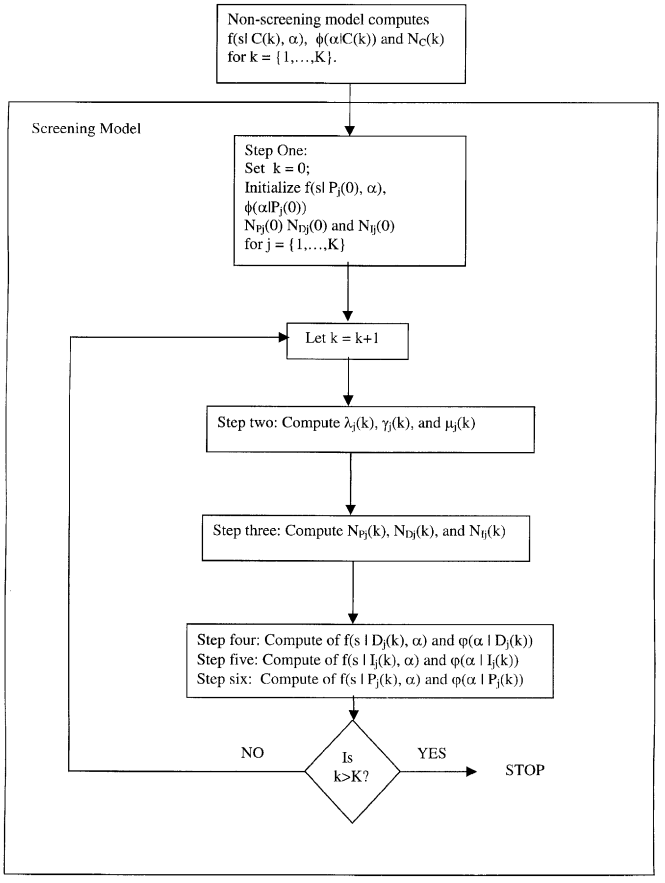

Fig. 3. Flowchart of the screening algorithm illustrated as the six-step procedure described in Section 3.1.2.

3.1.2.1. Step 1: Initialization. Time is set to year 0. The number of women in $P_j(0)$ is represented by $N_{P_j}(0)$. $N_{P_j}(0) = N_C(j)$ for $j = \{1, \ldots, K\}$, where $N_C(j)$ is the number of breast cancer patients in the non-screened cohort who are clinically detected in year j. The number of women in $D_j(0)$, represented by $N_{D_j}(0)$, is zero; and the number of women in $I_j(0)$, represented by $N_{I_j}(0)$, is zero.

The initial joint distribution of tumor size and doubling time among patients who are in $P_j(0)$ is represented by $\chi(s, \alpha \,|\, P_j(0))$. Using Bayes theorem, it can be expressed as

$$\chi(s, \alpha \,|\, P_j(0)) = f(s \,|\, P_j(0), \alpha)\varphi(\alpha \,|\, P_j(0)), \tag{10}$$

where $f(s \,|\, P_j(0), \alpha)$ represents the initial size distribution among patients in $P_j(0)$ with doubling time α; and $\varphi(\alpha \,|\, P_j(0))$ represents the initial doubling distribution among patients in $P_j(0)$. This section describes how to compute $f(s \,|\, P_j(0), \alpha)$ and $\varphi(\alpha \,|\, P_j(0))$.

The initial tumor size distribution among patients in $P_j(0)$ with doubling time α can be expressed as

$$f(s \,|\, P_j(0), \alpha) = \frac{1}{\beta_{-j}(\alpha)} f\left(\frac{s}{\beta_{-j}(\alpha)} \,\middle|\, C(j), \alpha \right) \quad \text{for } j = \{1, \ldots, K\}, \tag{11}$$

where $\beta_{-j}(\alpha) = \exp(-j \ln 2/(3\alpha))$ and $f(s|C(j),\alpha)$ is the size distribution among patients with doubling time α in the non-screened cohort who are clinically detected in year j. If patients in the jth preclinical state were never screened, they would be clinically detected with breast cancer in year j. Therefore, the initial tumor size distribution in $P_j(0)$ is obtained by projecting the size distribution among non-screened patients who were clinically detected in year j backwards in time by j years. This is performed by the scaling factor $\beta_{-j}(\alpha)$. The derivation of Eq. (11) is given in Appendix A.1.

The initial doubling time distribution for $P_j(0)$ is equivalent to the doubling time distribution among the non-screened patients who were clinically detected with breast cancer by the end of year j. It is expressed as

$$\varphi(\alpha|P_j(0)) = \varphi(\alpha|C(j)) \quad \text{for } j = \{1,\ldots,K\}. \tag{12}$$

This equivalence follows from the assumption that the doubling time does not change over time. While this assumption may not hold from the time of tumor onset, it may be reasonable over a limited number of years preceding clinical detection.

3.1.2.2. Step 2: Compute the state-transition probabilities at year k

3.1.2.2.1. Computing $\lambda_j(k)$. The probability of transitioning from $P_j(k-1)$ to $D_j(k)$ is represented by $\lambda_j(k)$. It can be expressed as $\text{Prob}[D_j(k)|P_j(k-1)]$. It is zero if screening is not offered in year k. If screening is offered in year k it can be re-expressed in terms of $f(s|P_j(k-1),\alpha)$ and $\varphi(\alpha|P_j(k-1))$ as follows:

$$\lambda_j(k) = \begin{cases} \int_0^\infty \int_0^\infty T(s) f(s|P_j(k-1),\alpha)\,\mathrm{d}s\,\varphi(\alpha|P_j(k-1))\,\mathrm{d}\alpha & \text{for } j \geqslant k, \\ 0 & \text{for } j < k, \end{cases} \tag{13}$$

where $T(s)$ is the probability that the screening exam detects a tumor of size s. It is assumed that screening occurs at the start of year k and that the distributions of tumor size and doubling time in the preclinical states at the start of year k are equivalent to the distributions of tumor size and doubling time at the end of year $k-1$. The transition probability $\lambda_j(k)$ is obtained by multiplying the tumor size distribution in the jth preclinical group at the time of screening, $f(s|P_j(k-1),\alpha)$, by the probability of detection, $T(s)$, and integrating over all sizes. The additional integration over doubling time is included because the size distribution in the integrand is conditioned on doubling time. The derivation of Eq. (13) is given in Appendix A.2.

The transition probability $\lambda_j(k)$ is zero for $j < k$ because patients in the jth preclinical state became interval patients by the end of year j if they had not been screen detected earlier. In other words, screening at the start of year k can only detect patients from jth preclinical state where $j \geqslant k$.

If screening is offered at the start of year k, then the probability that patients with doubling time α transition from $P_j(k-1)$ to $D_j(k)$ can be expressed as

$$\lambda_{j\alpha}(k) = \begin{cases} \int_0^\infty T(s) f(s|P_j(k-1),\alpha)\,\mathrm{d}s & \text{for } j \geqslant k, \\ 0 & \text{for } j < k. \end{cases} \tag{14}$$

This quantity will be useful for later equations.

3.1.2.2.2. Computing $\gamma_j(k)$. The probability of transitioning from $P_j(k-1)$ to $I_j(k)$ is represented by $\gamma_j(k)$. It can be expressed as

$$\gamma_j(k) = \text{Prob}[I_j(k) \,|\, P_j(k-1)] = \begin{cases} 1 - \lambda_j(k) & \text{for } j = k, \\ 0 & \text{for } j \neq k. \end{cases} \tag{15}$$

If screening is not offered in year k, then $\lambda_j(k) = 0$ and $\gamma_j(k) = 1$, that is, all the patients in $P_j(k-1)$ become interval patients by the end of year k. If screening is offered in year k, then only the patients in $P_j(k-1)$ who have not been screen detected become interval patients by the end of year k. $\gamma_j(k)$ is zero for all $j \neq k$ because patients only in the jth preclinical state can become clinically detected in year j.

3.1.2.2.3. Computing $\mu_j(k)$. The probability of transitioning from $P_j(k-1)$ to $P_j(k)$ is represented by $\mu_j(k)$. It can be expressed as

$$\mu_j(k) = \text{Prob}[P_j(k) \,|\, P_j(k-1)] = \begin{cases} 1 - \lambda_j(k) & \text{for } j > k, \\ 0 & \text{for } j \leqslant k. \end{cases} \tag{16}$$

If screening is not offered at the start of year k, then patients in $P_j(k-1)$ transition to $P_j(k)$ for $j > k$. If screening is offered in year k, then only preclinical patients who were not screen detected remain in P_j for $j > k$. When $j \leqslant k$, there are no patients in $P_j(k)$ and $\mu_j(k)$ is zero. These preclinical patients have either become screened detected or interval patients.

3.1.2.3. Step 3: Compute the number of patients in each state by the end of year k. The number of women in $P_j(k)$, $D_j(k)$, and $I_j(k)$ is represented by $N_{P_j}(k)$, $N_{D_j}(k)$ and $N_{I_j}(k)$, respectively. Given the transition probabilities $\lambda_j(k)$, $\gamma_j(k)$ and $\mu_j(k)$, these quantities can be determined by

$$\begin{aligned} N_{P_j}(k) &= \mu_j(k) N_{P_j}(k-1), \\ N_{D_j}(k) &= \lambda_j(k) N_{P_j}(k-1), \\ N_{I_j}(k) &= \gamma_j(k) N_{P_j}(k-1), \end{aligned} \tag{17}$$

for $j = \{1, \ldots, K\}$.

3.1.2.4. Step 4: Compute the joint distribution of tumor size and doubling time among screen detected patients in year k. The joint distribution of tumor size and doubling time in $D_j(k)$ is represented by $\chi(s, \alpha \,|\, D_j(k))$. Using Bayes theorem, it can be expressed as

$$\chi(s, \alpha \,|\, D_j(k)) = f(s \,|\, D_j(k), \alpha) \varphi(\alpha \,|\, D_j(k)), \tag{18}$$

where $f(s \,|\, D_j(k), \alpha)$ represents the tumor size distribution among patients with doubling time α in $D_j(k)$; and $\varphi(\alpha \,|\, D_j(k))$ represents the doubling time distribution among patients in $D_j(k)$. This section describes how to compute $f(s \,|\, D_j(k), \alpha)$ and $\varphi(\alpha \,|\, D_j(k))$ when screening in year k. The distributions are null when screening is not offered in year k.

When screening is offered, it is assumed that screening occurs at the start of year k and the tumor size and doubling time distributions at the start of year k are equivalent to the distributions at the end of year $k-1$. With these assumptions, the tumor size distribution among patients with the doubling time α in $D_j(k)$ can be expressed as

$$f(s \,|\, D_j(k), \alpha) = \begin{cases} \left(\frac{1}{\lambda_{j\alpha}(k)} \right) T(s) f(s \,|\, P_j(k-1), \alpha) & \text{for } j \geqslant k, \\ 0 & \text{for } j < k. \end{cases} \tag{19}$$

For $j \geqslant k$, this expression shows that the tumor size distribution in jth preclinical state at the time of screening, namely $f(s|P_j(k-1),\alpha)$, is multiplied by the probability of detection, $T(s)$, then normalized by $1/\lambda_{j\alpha}(k)$. For $j < k$, the distribution is null because no patients are left in the jth preclinical state. The derivation of Eq. (19) is given in Appendix A.3.

The doubling time distribution among patients in $D_j(k)$ is

$$\varphi(\alpha|D_j(k)) = \begin{cases} \left(\frac{\lambda_{j\alpha}(k)}{\lambda_j(k)}\right)\varphi(\alpha|P_j(k-1)) & \text{for } j \geqslant k, \\ 0 & \text{for } j < k. \end{cases} \tag{20}$$

For $j \geqslant k$, this expression shows that the doubling time distribution in the jth preclinical state at the time of screening, $\varphi(\alpha|P_j(k-1))$, is multiplied by the probability of transitioning to screen detection, $\lambda_{j\alpha}(k)$, and then normalized by $\lambda_j(k)$. For $j < k$, the distribution is null because no patients are left in the jth preclinical state. The derivation of Eq. (20) is given in Appendix A.4.

3.1.2.5. Step 5: Compute the joint distribution of tumor size and doubling time among interval patients in year k. The joint distribution of tumor size and doubling time in $I_j(k)$ is represented by $\chi(s,\alpha|I_j(k))$. Using Bayes theorem, it can be expressed as

$$\chi(s,\alpha|I_j(k)) = f(s|I_j(k),\alpha)\varphi(\alpha|I_j(k)), \tag{21}$$

where $f(s|I_j(k),\alpha)$ represents the tumor size distribution among patients in $I_j(k)$ with doubling time α; and $\varphi(\alpha|I_j(k))$ represents the distribution of doubling time among patients in $I_j(k)$. This section describes how to compute $f(s|P_j(k),\alpha)$ and $\varphi(\alpha|P_j(k))$ when screening is offered in year k (Case A) and when screening is not offered in year k (Case B).

3.1.2.5.1. Case A: Screening is offered at the start of year k. If screening is offered, the distribution $f(s|I_j(k),\alpha)$ can be expressed as

$$f(s|I_j(k),\alpha) = \begin{cases} \frac{1}{\beta_1(\alpha)(1-\lambda_{j\alpha}(k))}\left(1 - T\left(\frac{s}{\beta_1(\alpha)}\right)\right) f\left(\frac{s}{\beta_1(\alpha)}\middle| P_j(k-1),\alpha\right) & \text{for } j = k, \\ 0 & \text{for } j \neq k, \end{cases} \tag{22}$$

where $\beta_1(\alpha) = \exp(\ln 2/(3\alpha))$. At year k only the patients of the kth preclinical state who have not been screen detected become interval patients. It is assumed that interval patients are diagnosed at the end of the year k and screening occurs at the start of the year k. Hence, tumors remaining in the kth preclinical state immediately following screening grow for an additional year before becoming detected. The effect of their growth on the tumor size distribution at detection is captured above by the scaling term $\beta_1(\alpha)$. The derivation of Eq. (22) is given in Appendix A.5.
If screening is offered, then $\varphi(\alpha|I_j(k))$ can be expressed as

$$\varphi(\alpha|I(k)) = \begin{cases} \left(\frac{1-\lambda_{j\alpha}(k)}{1-\lambda_j(k)}\right)\varphi(\alpha|P_j(k-1)) & \text{for } j = k, \\ 0 & \text{for } j \neq k. \end{cases} \tag{23}$$

At year k, only the component of the doubling time distribution in the kth preclinical group that has not been screen detected becomes clinically detected.

3.1.2.5.2. Case B: Screening is not offered at the start of year k. If screening is not offered, then $f(s|I_j(k),\alpha)$ can be expressed as

$$f(s\,|\,I_j(k),\alpha)=\begin{cases}\frac{1}{\beta_1(\alpha)}f\left(\frac{s}{\beta_1(\alpha)}\,\middle|\,P_j(k-1),\alpha\right) & \text{for } j=k,\\ 0 & \text{for } j\neq k,\end{cases} \tag{24}$$

where $\beta_1(\alpha)=\exp(\ln 2/(3\alpha))$. All the patients in the kth preclinical state become interval patients by the end of year k. The tumors of patients in $P_j(k-1)$ grow for an additional year before becoming clinically detected, therefore the distribution $f(s\,|\,P_k(k-1),\alpha)$ is scaled by $\beta_1(\alpha)$.
If screening is not offered, then $\varphi(\alpha\,|\,I_j(k))$ can be expressed as

$$\varphi(\alpha\,|\,I_j(k))=\begin{cases}\varphi(\alpha\,|\,P_j(k-1)) & \text{for } j=k,\\ 0 & \text{for } j\neq k.\end{cases} \tag{25}$$

The doubling time distribution in kth preclinical state at the end of year $k-1$ becomes the doubling time distribution for the interval patients at the end of year k.

3.1.2.6. Step 6: Compute the joint distribution of tumor size and doubling time among the preclinical in year k. The joint distribution of tumor size and doubling time in $P_j(k)$ is represented by $\chi(s,\alpha\,|\,P_j(k))$. Using Bayes theorem, it can be expressed as

$$\chi(s,\alpha\,|\,P_j(k))=f(s\,|\,P_j(k),\alpha)\varphi(\alpha\,|\,P_j(k)), \tag{26}$$

where $f(s\,|\,P_j(k),\alpha)$ represents the tumor size distribution among patients in $P_j(k)$ with doubling time α; and $\varphi(\alpha\,|\,P_j(k))$ represents the distribution of doubling time among patients in $P_j(k)$. This section describes how to compute $f(s\,|\,P_j(k),\alpha)$ and $\varphi(\alpha\,|\,P_j(k))$ when screening is offered in year k (Case A) and when screening is not offered in year k (Case B).

3.1.2.6.1. Case A: Screening is offered at the start of year k. If screening is offered, then $f(s\,|\,P_j(k),\alpha)$ can be expressed as

$$f(s\,|\,P_j(k),\alpha)=\begin{cases}\frac{1}{\beta_1(\alpha)(1-\lambda_{j\alpha}(k))}\left(1-T\left(\frac{s}{\beta_1(\alpha)}\right)\right)f\left(\frac{s}{\beta_1(\alpha)}\,\middle|\,P_j(k-1),\alpha\right) & \text{for } j>k,\\ 0 & \text{for } j\leqslant k,\end{cases} \tag{27}$$

where $\beta_1(\alpha)=\exp(\ln 2/(3\alpha))$. It is assumed screening occurs at the start of year k and all the patients in the preclinical states j where $j>k$ who are not screen detected remain in their respective preclinical states till the end of year k. This equation is similar to Eq. (22), except that patients who are not screen detected become preclinical patients as opposed to interval patients. This equation is zero for $j=k$, since patients who are not screen detected in the kth preclinical group become interval patients.

If screening is offered, then $\varphi(\alpha\,|\,P_j(k))$ can be expressed as

$$\varphi(\alpha\,|\,P_j(k))=\begin{cases}\left(\frac{1-\lambda_j(k\,|\,\alpha)}{1-\lambda_j(k)}\right)\varphi(\alpha\,|\,P_j(k-1)) & \text{for } j>k,\\ 0 & \text{for } j\leqslant k.\end{cases} \tag{28}$$

This expression is similar to Eq. (23), except that patients who are not screen detected become preclinical patients as opposed to interval patients.

3.1.2.6.2. Case B: Screening is not offered in year k. If screening is not offered, then $f(s\,|\,P_j(k),\alpha)$ can be expressed as

$$f(s\,|\,P_j(k),\alpha)=\begin{cases}\frac{1}{\beta_1(\alpha)}f\left(\frac{s}{\beta_1(\alpha)}\,|\,P_j(k-1),\alpha\right) & \text{for } j>k,\\ 0 & \text{for } j\leqslant k,\end{cases} \tag{29}$$

where $\beta_1(\alpha)=\exp(\ln 2/(3\alpha))$. This expression is similar to Eq. (24), except that patients who are not screen detected become preclinical patients as opposed to interval patients.

If screening is not offered, then $\varphi(\alpha\,|\,P_j(k))$ can be expressed as

$$\varphi(\alpha\,|\,P_j(k))=\begin{cases}\varphi(\alpha\,|\,P_j(k-1)) & \text{for } j>k,\\ 0 & \text{for } j\leqslant k.\end{cases} \tag{30}$$

This expression is similar to Eq. (25), except that patients who are not screen detected become preclinical patients as opposed to interval patients.

3.2. Sensitivity and leadtime of screening

The sensitivity of screening in year k, represented by $\zeta(k)$, is defined as the number of screen detected patients in year k divided by the sum of the number of screen detected in year k and the number of interval patients in year k. It can be expressed as

$$\zeta(k)=\frac{\sum_{j=1}^{K}N_{D_j}(k)}{\sum_{j=1}^{K}N_{D_j}(k)+N_{I_k}(k)}. \tag{31}$$

The leadtime of screening is defined as the time interval between the time a patient is screen detected and the time the patient would have been clinically detected had they not been screened. For screen detected patients in $D_j(k)$, the leadtime, represented by L, would be $(j-k+1)$. These patients would have been detected at the end of year j but are instead screen detected at the start of year k $(k<j)$, hence the leadtime is $(j-k+1)$ as illustrated in Fig. 4. The minimum leadtime is 1 year (when $j=k$) and maximum leadtime is K years (when $k=1$ and $j=K$).

The probability of leadtime l is

$$\text{Prob}[L=l]=\frac{\sum_{k=1}^{K}\sum_{j=k}^{K}N_{D_j}(k)\boldsymbol{I}[(j-k+1)=l]}{\sum_{k=1}^{K}\sum_{j=k}^{K}N_{D_j}(k)}\quad \text{for } l=\{1,\ldots,K\}, \tag{32}$$

where the indicator function $\boldsymbol{I}$ is one when $(j-k+1)=l$; otherwise it is zero. The probability of leadtime l is the sum of all the screen detected patients whose leadtime is l, divided by all the screen detected patients. The sensitivity and leadtime of screening can also be formulated for a specific doubling time.

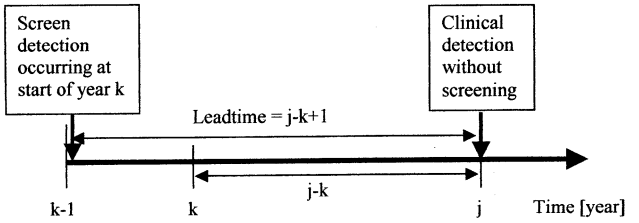

Fig. 4. Illustration of the leadtime calculation for a patient who is screen detected in year k and who would have been clinically detected in year j without screening. Screening in year k occurs at the start of year k, therefore, the leadtime is $j-k+1$ years.

4. Results

The screening algorithm is programmed to simulate a hypothetical cohort over a period of 20 years. First the cohort is simulated without screening, then the cohort is simulated with screening. When the cohort is simulated without screening, the annual breast cancer incidence is constant (represented by N_0) and the annual joint distribution of tumor size and growth rate is constant. The annual mean tumor size is 3.0 cm in diameter. This mean tumor size approximates the mean tumor size in the SEER database before screening was introduced (prior to calendar year 1982) [19]. The annual mean doubling time is 5.4 months and the annual standard deviation of the doubling time is 4 months; these figures are based on limited clinical data [16]. The mean tumor size, the mean doubling time and the standard deviation of the doubling time are sufficient to specify the model described in Section 3.1.1 (parameter values $r = 1.7$, $a = 0.0073$ and $b = 0.00022$). The corresponding annual tumor size distribution is given by Fig. 5(a), the annual tumor size distribution conditioned on the growth rate is given by Fig. 5(b), the annual doubling time distribution is given by Fig. 5(c) and the annual joint distribution of tumor size and growth rate is given by Fig. 5(d).

The hypothetical cohort is simulated with screening such that screening starts in year 1, continues on an annual basis until year 10, and no screening is offered in years 11–20. The detection threshold of the screening exam has a normal distribution with mean of 1 cm and standard deviation of 0.2 cm. The distribution of detection threshold is assumed to approximate that of screening mammography. To initialize the screening algorithm, 20 preclinical groups are created as described in Section 3.1.2. The number of breast cancer patients in jth preclinical group at year 0 is N_0 because this number of breast cancer patients who would be clinically detected in year j if screening were never offered. The initial doubling time distribution in each preclinical group is equivalent to the doubling time distribution shown in Fig. 5(c). The initial tumor size distribution conditioned on the doubling time, namely $f(s|P_j(0), \alpha)$ for $j = \{1, \ldots, 20\}$, is obtained by scaling the corresponding conditional distributions in Fig. 5(b), as described in Section 3.1.2 (step 1).

4.1. Sensitivity of screening

A plot of the annual incidence of screen detected and interval patients over the 20-year period is given in Fig. 6. The incidence of screen detected patients is largest at the first round of screening. It quickly reaches a steady-state value while screening is still offered. In steady state, the annual incidence of the screen detected and interval patients is N_0. When screening stops, breast cancer patients are clinically detected. The annual incidence decreases immediately after screening stops and then gradually rises to its initial level N_0.

The sensitivity of screening is largest in the first round of screening (83%) then decreases to a steady state value (72%) in subsequent rounds of screening. Later we show that the sensitivity is a function of the growth rate.

4.2. Joint distribution of tumor size and doubling times

At each year k, joint distributions of tumor size and doubling times are computed for the 20 preclinical states, the 20 screen detected states and the 20 interval states at each year k; this yields a

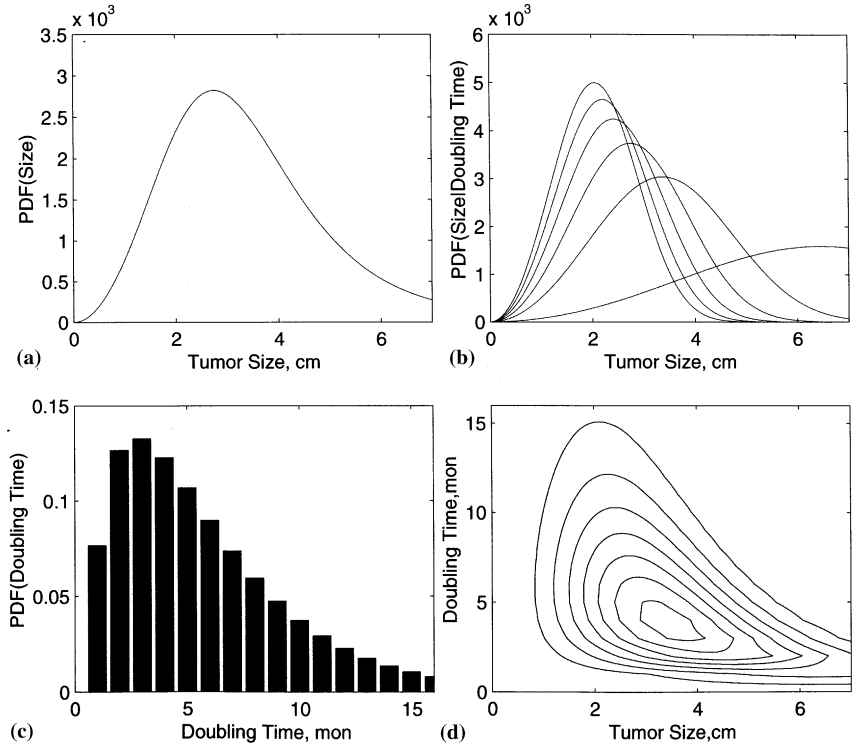

Fig. 5. Annual breast cancer outcomes for the non-screened cohort: (a) tumor size distribution; (b) tumor size distribution conditioned on doubling time, for doubling times of 1 month (broadest curve), 4 months, 7 months, 10 months, 13 months, 16 months (narrowest curve); (c) doubling time distribution; (d) joint distribution of tumor size and doubling time.

total of 60 joint distributions. Over a 20-year period, 1200 joint distributions are generated. These results are summarized below in terms of the annual mean tumor size, annual mean tumor growth rate and the time-averaged joint distribution of tumor size and doubling time.

The mean tumor size among the screen detected patients in the first round of screening is 1.52 cm. In subsequent screening rounds, the annual mean tumor size of the screen detected patients is roughly constant at 1.18 cm. The annual mean tumor size for the interval patients is relatively constant at 2.7 cm over the screening period. Compared to the screen detected patients, the interval patients are detected with larger tumors.

The mean doubling time among the screened detected patients in the first round of screening is 8.6 months. For subsequent screening rounds, the annual mean doubling time of the screen detected patients decreases to a constant of 7.0 months. The annual mean tumor growth rate among the interval patients is relatively constant over the screening period. It is approximately 3.2 months. Compared to the screen detected patients, the interval patients have faster growth rates.

The annual joint distributions of tumor size and growth rate averaged over the screening period (years 1–10) are referred to as the time-averaged joint distribution. The time averaged joint distribution for the screen detected patients is shown in Fig. 7(a). The slower growing tumors are

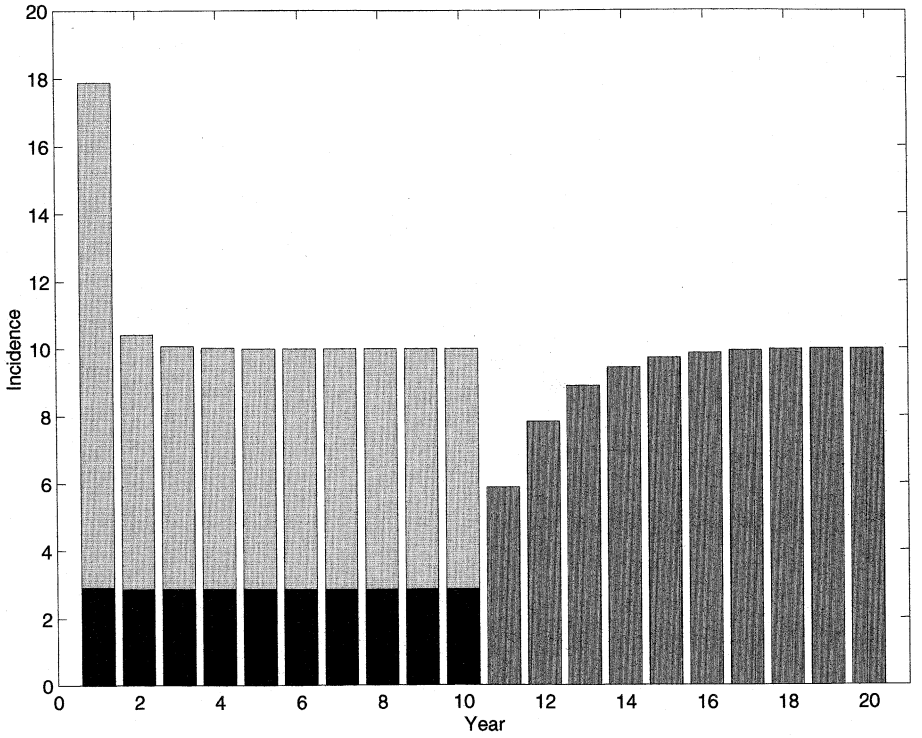

Fig. 6. The annual incidence of breast cancer in the screened cohort. The bars are color-coded to distinguish among the screen detected patients (light grey), interval patients (dark grey) and clinically detected patients (medium grey). The interval patients and clinically detected patients have a subtle difference: the interval patients are diagnosed while screening is being offered, whereas the clinically detected patients are diagnosed after screening end. ($N_0 = 10$.)

detected closer to the detection threshold of the screening examination than the faster growing tumors. The time-averaged joint distribution of the doubling time and the tumor size for the interval patients is shown in Fig. 7(b). The larger-sized interval tumors have faster doubling times than the smaller-sized interval tumors. The time-averaged distributions of tumor size for the screened detected and interval patients are shown in Figs. 7(c) and (d), respectively. The time-averaged distributions of doubling time for the screen detected and intervals patients are shown in Figs. 7(e) and (f), respectively.

4.3. Comparison between the non-screened and screened patients

If annual screening is extended over the 20 year period, then the joint distribution of tumor size and doubling time for the non-screened patients can be decomposed into the components for the screen detected patients and the interval patients. This decomposition is shown in Fig. 8(a).

The tumor size distribution for the non-screened patients is shown in Fig. 5(a). The components of this distribution for the screen detected and interval patients are shown in Fig. 8(b). Most of the smallest tumors ($\leqslant 1$ cm) are missed because they are below the detection threshold of the

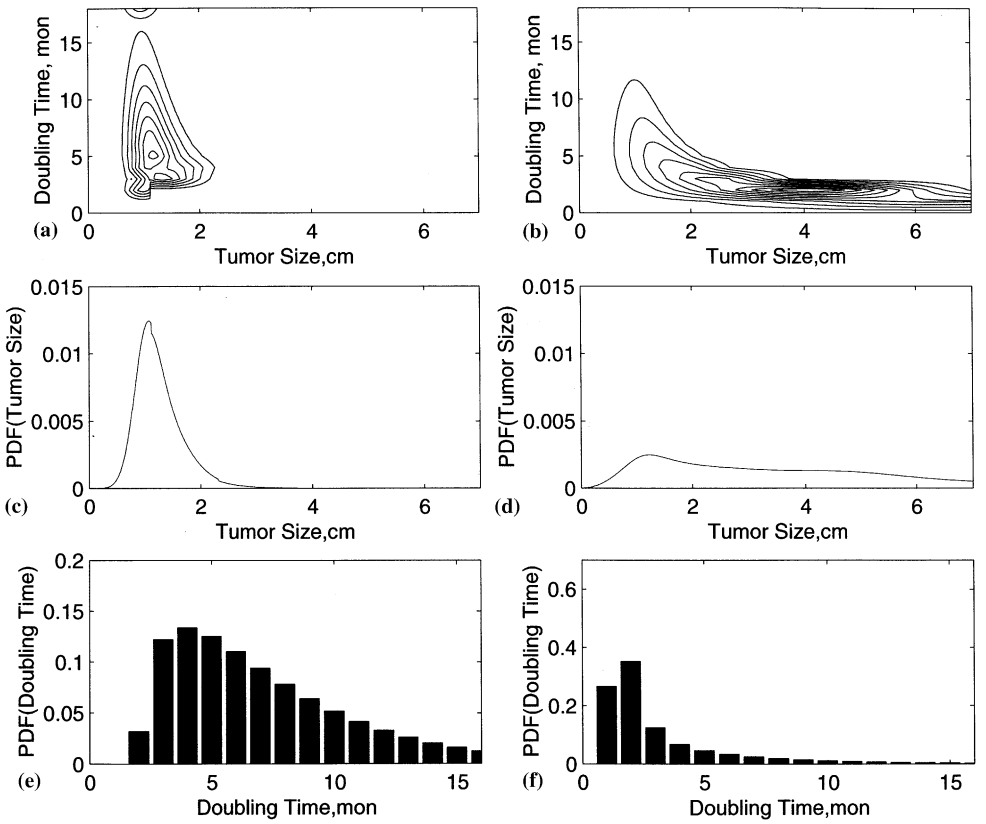

Fig. 7. Comparison between screen-detected patients and interval patients: (a) The joint distribution of the tumor size and doubling time among the screen-detected patients; (b) The joint distribution of the tumor size and doubling time among the interval patients; (c) The tumor size distribution among the screen detected patients; (d) The tumor size distribution among the interval patients; (e) The doubling time distribution among the screen detected patients; (f) The doubling time distribution among the interval patients.

screening exam when they become clinically detected, even though they have the slowest growth rate.

The doubling time distribution for the non-screened patients is shown in Fig. 5(c). The components of this distribution for the screen detected and interval patients are shown in Fig. 8(c). The probability of screen detection is approximately zero for tumors with doubling time of 1 month, 20% with 2 month, 73% with 3 month, 84% with 4 month, 88% with 5 month, and 92% or greater for tumors with doubling times of 6 months or greater, as shown in Fig. 8(d). The probability of screen detection increases as the doubling time increases.

4.4. Leadtime distribution

For each screening round, the screen detected patients can be decomposed into the preclinical groups from which they were detected, as shown in Figs. 9(a) and (b). For a screening exam in year k, the screen detected patients can come from preclinical groups P_k–P_{10}. For example, in the

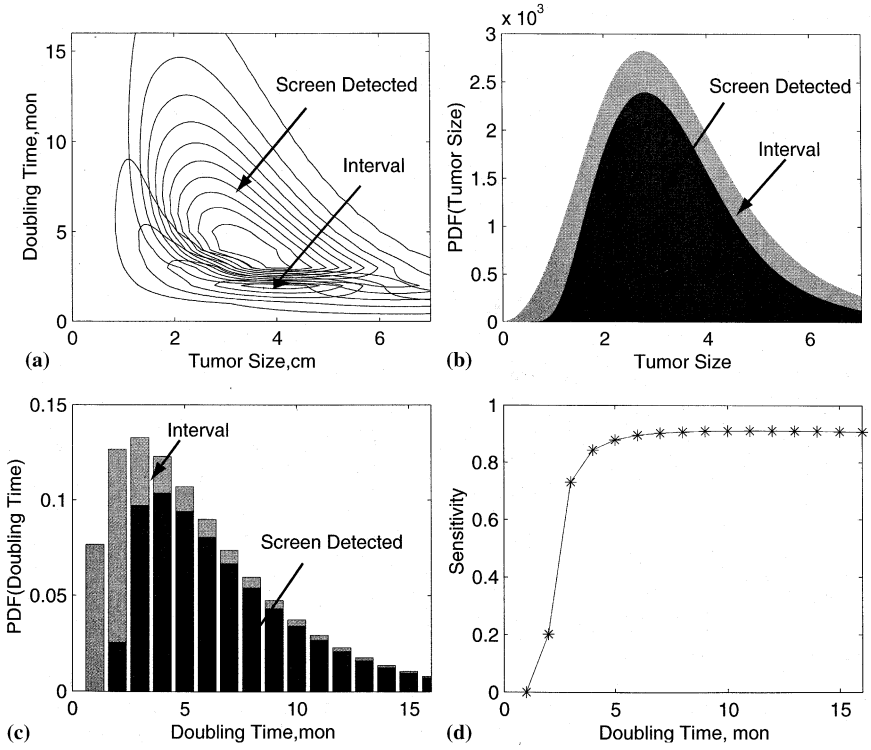

Fig. 8. Decomposition of non-screened distribution into screen-detected and interval components: (a) Decomposition of the joint distribution of detected tumor size and doubling time of the non-screened cohort into screen detected and interval components; (b) Decomposition of the tumor size distribution in the non-screened cohort into screen-detected and interval components; the light-grey area corresponds to the interval component and the dark-grey area corresponds to the screen detected component; (c) Decomposition of the doubling time distribution into the screen-detected and interval components; the light-grey area corresponds to the interval component and the dark-grey area corresponds to the screen detected component; (d) The sensitivity of annual screening as a function of the doubling time.

first round, the screen detected patients are composed of 70% from P_1, 40% from P_2, 20% from P_3, 9.8% from P_4, 4.6% from P_5, and less than 3% from each preclinical state P_5–P_{10}. Alternatively, this decomposition can be described in terms of leadtime as follows: 47% have a 1-year leadtime, 26% have a 2-year leadtime, 13% have a 3-year leadtime, and 14% have a leadtime of four years or more. The mean leadtime for the first round of screen detected patients is 2.0 years. The mean leadtime in screening in the steady-state phase is 2.2 years.

The leadtime distribution conditioned on the doubling is given in Fig. 10(a). Among the screen detected patients with 2-month doubling times, the leadtime is 1 year. Among screen detected patients with 18-month doubling times, 15% have a 1-year leadtime, 16% have a 2-year leadtime, 17% have a 3-year leadtime, 16% have a 4-year leadtime, and the remaining 36% have a leadtime of 5 years for more. The mean lead time conditioned on the growth rate is shown in Fig. 10(b). The mean leadtime increases from 1 year to 3.7 years as the doubling time increases from 2 months to 18 months. Hence, the slow growing tumors are not only more likely to be screen detected, but they have a longer leadtime than the faster growing tumors that are screen detected.

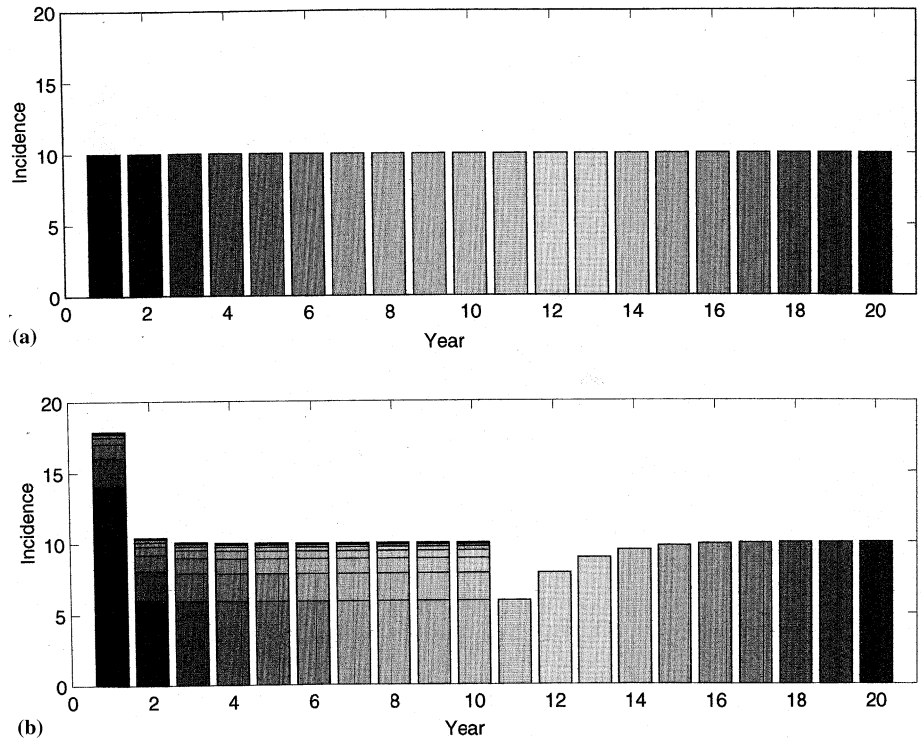

Fig. 9. Illustration of leadtime: (a) Initial incidence among 20 preclinical states, where each state is color-coded; (b) annual incidence after screening, where color-coding is used to illustrate the decomposition of the screen-detected and interval patients into the preclinical states from which they were detected. ($N_0 = 10$.)

4.5. Sensitivity analysis

In a one-way sensitivity analysis, the effect of the doubling time of the non-screened cohort is investigated. When the mean annual doubling time for the non-screened cohort decreases to 3.5 months (from 5.4 months), the steady state sensitivity of annual screening decreases to 54% (from 72%). When the mean annual doubling time increases to 7 months, the annual steady state sensitivity increases by 81%. The sensitivity increases as the proportion of slow growing tumors in the non-screened cohort increases.

Finally, the tumor size and doubling time distributions of the non-screened population are assumed uncorrelated as expressed by Eq. (3). The steady state sensitivity is slightly higher at 74%. However, the tumor size and doubling times are correlated in the screen detected and interval patients. Larger screen detected and interval tumors have higher growth rates.

5. Discussion

This paper presents a mathematical algorithm that computes the joint distribution of the tumor sizes and tumor growth rates detected by breast cancer screening, the sensitivity and leadtime of screening. Based on assumptions of tumor size and growth rate of breast cancer in a non-screened

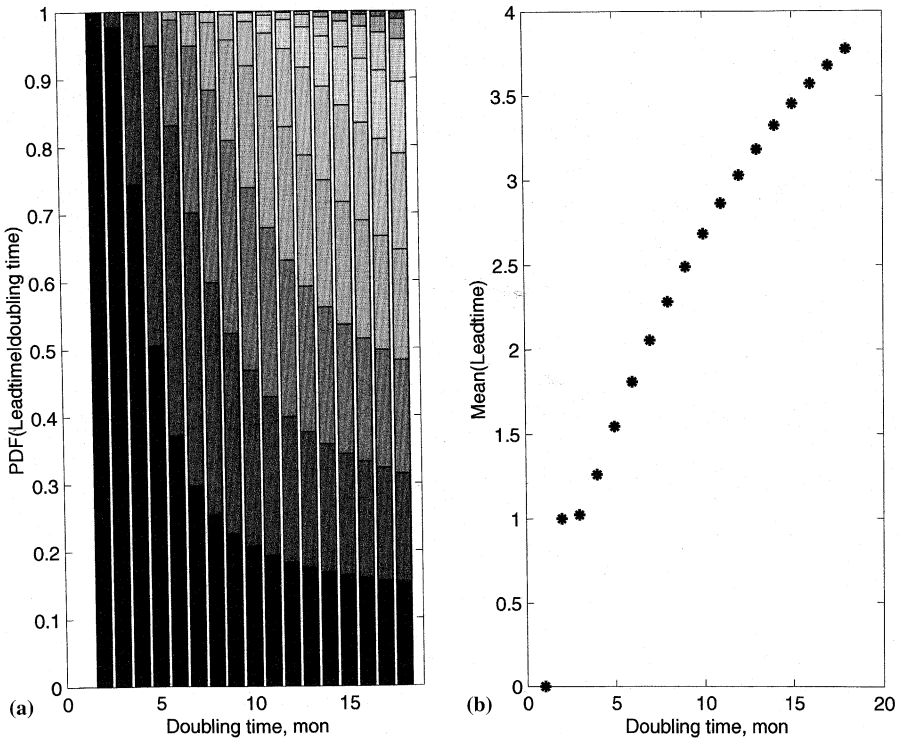

Fig. 10. (a) Leadtime distribution as a function of the doubling time. The leadtime is color-coded as follows: for 1 year leadtime to seven year lead leadtime, the corresponding colors range from dark grey to light grey; then the colors get incrementally darker for the small group of leadtimes greater than seven years. (b) Mean leadtime as a function of the doubling time.

cohort, the algorithm tracks tumor growth backwards in time from the time the tumor would be clinically detected. It does not track tumor growth forward in time from the time of onset as other screening algorithms. The main advantage of using the backward tracking method is that the time of clinical detection in the non-screened cohort is observable, whereas the time of tumor onset is not observable. Another advantage of the backward tracking method is that it does not require knowledge of tumor growth from the time of onset to the time of detection. The backward tracking method only requires knowledge of tumor growth during the tumor's preclinical detectable phase, that is, in the time period between the time the tumor is screened detectable and the time it is symptomatically detected. During this phase, a particular tumor growth function may be more easily justified, as opposed to justifying a growth function that extends from the time of onset to the time of detection. We assumed exponential tumor growth, since exponential growth has been observed around the time tumors are detected. The algorithm also can be generalized for alternative tumor growth functions [20,21].

The algorithm can be used to simulate a variety of screening programs. The following parameters can vary over time: the interval between screening examinations, the detection probability of the screening exam, and the incidence of breast cancer in the non-screened cohort, the joint distribution of detected tumor size and tumor growth rate in the non-screened cohort, and

the growth function of breast cancer. Because the algorithm dynamically tracks the outcomes of the cohort, it provides both the transient and steady state outcomes of screening.

The algorithm was used to simulate the outcomes of screening under conditions assumed to approximate annual breast cancer screening with conventional mammography. The simulation was performed with numerous simplifications: a constant annual incidence of breast cancer patients in the non-screened cohort, a constant detection threshold of the screen test, an exponential tumor growth function, a constant annual tumor size and growth rate distribution in the non-screened cohort.

The algorithm produces the expected curve for breast cancer incidence. The incidence is large at the first screen round, then quickly reaches a steady state. When screening stops, the incidence dips then climbs back to its steady state value. The screen detected tumors are shifted to smaller sizes, close to the detection threshold of the screening test. The algorithm also provides numerous unobservable but intuitively reasonable results. The earlier rounds of screening have a higher percentage of slow growing tumors. The screeen detected tumors are predominately slower growing. The slower growing tumors are not only more likely to be screen detected, but they are more likely to be associated with a longer leadtime than the fast growing screen-detected tumors. Among the fast growing screen-detected tumors most are detected with a mean leadtime of 1 year whereas the slower growing tumors are detected with a mean leadtime of 3.7 years. Compared to the screen detected patients, the interval patients have faster growing and larger tumors. The interval patients also have the slow growing tumors that are missed because these tumors are clinically detected below the detection threshold of the screening examination.

The model predicted a sensitivity for annual screening of 82% in the first round and 74% in the steady state phase. This sensitivity is slightly lower than that reported in some clinical trials of annual screening mammography [22–24]. When the doubling time distribution in the non-screened cohort had a higher proportion of slower growing tumors, the sensitivity increased.

In summary, this manuscript presents a mathematical algorithm that computes tumor sizes and growth rates detected by screening based on a model of the natural history of breast cancer in a non-screened cohort. The algorithm simulates screening by tracking tumor growth backwards in time starting from the time it would have been clinically detected. The algorithm was implemented. It demonstrated that the screen detected tumors are smaller in size and slower in growth rate than interval tumors. Furthermore, the slower-growing screen detected tumors have a longer leadtime than the faster growing screen-detected tumors. This algorithm may be valuable in simulating intermediate outcomes for a variety of screening trials with a wide range of detection thresholds and screening intervals that would not be feasible to analyze with clinical trials.

Appendix A

A.1. Derivation of Eq. (11)

Let $\{s \mid P_j(0), \alpha\}$ represent the initial tumor size among preclinical patients in $P_j(0)$ whose doubling time is α. Let $\{s \mid C(j), \alpha\}$ represent the tumor size of the same patients but when they are not screened and their tumor is instead clinically detected in year j. Assuming that tumor volume grows exponentially, then

$$\{s\,|\,P_j(0),\alpha\} = \beta_{-j}(\alpha) * \{s\,|\,C(j),\alpha\}, \quad \text{where } \beta_{-j}(\alpha) = \exp(-j\ln 2/(3\alpha)).$$

If the distribution of $\{s\,|\,C(j),\alpha\}$ is $f(s\,|\,C(j),\alpha)$, then the distribution of $\{s\,|\,P_j(0),\alpha\}$ is $1/\beta_{-j}(\alpha)f(s/\beta_{-j}(\alpha)\,|\,C(j),\alpha)$.

A.2. Derivation of Eq. (13)

$$\lambda_{D_j}(k) \equiv P[D_j(k)\,|\,P_j(k-1)] = \int_0^\infty P[D_j(k)\,|\,P_j(k-1),\alpha]\varphi(\alpha\,|\,P_j(k-1))\,\mathrm{d}\alpha.$$

Substituting

$$P[D_j(k)\,|\,P_j(k-1),\alpha] = \int_0^\infty T(s)f(s\,|\,P_j(k-1),\alpha)\,\mathrm{d}s$$

yields

$$\lambda_{D_j}(k) = \int_0^\infty \int_0^\infty T(s)f_s(s\,|\,P_j(k),\alpha)\,\mathrm{d}s\varphi(\alpha\,|\,P_j(k))\,\mathrm{d}\alpha.$$

A.3. Derivation of Eq. (19)

For $j \geqslant k, f(s\,|\,D_j(k),\alpha)$

$$\begin{aligned}
&= f(s\,|\,D_j(k),P_j(k-1),\alpha)\\
&= f(s,D_j(k)\,|\,P_j(k-1),\alpha)/\mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha]\\
&= \mathrm{Prob}[D_j(k)\,|\,P_j(k-1),s,\alpha]/\mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha]f_s(s\,|\,P_j(k-1),\alpha).
\end{aligned}$$

Substituting $\mathrm{Prob}[D_j(k)\,|\,s,\ P_j(k-1),\alpha] = T(s)$ and $\mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha] = \lambda_{j\alpha}(k)$ yields $f(s\,|\,D_j(k),\alpha) = (1/\lambda_{j\alpha}(k))T(s)f_s(s\,|\,P_j(k-1),\alpha)$.

A.4. Derivation of Eq. (20)

$$\begin{aligned}
\varphi(\alpha\,|\,D_j(k)) &= \varphi(\alpha\,|\,D_j(k),P_j(k-1))\\
&= \varphi(\alpha,D_j(k)\,|\,P_j(k-1))/\mathrm{Prob}[D_j(k)\,|\,P_j(k-1)]\\
&= \varphi(\alpha\,|\,D_j(k-1))\mathrm{Prob}[D_j(k)\,|\,D_j(k-1),\alpha]/\mathrm{Prob}[D_j(k)\,|\,P_j(k-1)].
\end{aligned}$$

Substituting $\mathrm{Prob}[D_j(k)\,|\,D_j(k-1),\alpha] = \lambda_{j\alpha}(k)$ when $j > k$ and $\mathrm{Prob}[D_j(k)\,|\,P_j(k-1)] = \lambda_{Dj}(k)$ when $j > k$, gives $\varphi(\alpha\,|\,D_j(k)) = \lambda_{j\alpha}(k)/\lambda_j(k)\varphi(\alpha\,|\,P_j(k-1))$ for $j > k$.

A.5. Derivation of Eq. (22)

Screening is assumed to occur at the start of year k, and the tumor size in the preclinical group P_j at the time of screening is assumed to be $f_s(s\,|\,P_j(k-1),\alpha)$. In the moment following screening, the patients in the preclinical group P_j are those who were not screen detected.

Let year $k-1+\delta$ represent the moment following screening, such that δ is positive and close to zero. The tumor size distribution in preclinical group P_j in year $k-1+\delta$ is given by

$$
\begin{aligned}
&f(s\,|\,P_j(k-1+\delta),\alpha)\\
&\quad = f(s\,|\,P_j(k-1+\delta),P_j(k-1),\alpha)\\
&\quad = f(s,P_j(k-1+\delta)\,|\,P_j(k-1),\alpha)/\mathrm{Prob}[P_j(k-1+\delta)\,|\,P_j(k-1),\alpha]\\
&\quad = f(s\,|\,P_j(k-1),\alpha)\mathrm{Prob}[P_j(k-1+\delta)\,|\,s,P_j(k-1),\alpha]/\mathrm{Prob}[P_j(k-1+\delta)\,|\,P_j(k-1),\alpha].
\end{aligned}
$$

Substituting

$$\mathrm{Prob}[P_j(k-1+\delta)\,|\,s,P_j(k-1),\alpha] = (1-\mathrm{Prob}[D_j(k)\,|\,s,P_j(k-1),\alpha])$$

and

$$\mathrm{Prob}[P_j(k-1+\delta)\,|\,P_j(k-1),\alpha] = \mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha])$$

gives

$$
\begin{aligned}
&f(s\,|\,P_j(k-1+\delta),\alpha)\\
&\quad = (1-\mathrm{Prob}[D_j(k)\,|\,s,P_j(k-1),\alpha])f(s\,|\,P_j(k-1),\alpha)/(1-\mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha]).
\end{aligned}
$$

Substituting

$$\mathrm{Prob}[D_j(k)\,|\,s,P_j(k-1),\alpha] = T(s) \quad \text{and} \quad \mathrm{Prob}[D_j(k)\,|\,P_j(k-1),\alpha]) = \lambda_{j\alpha}(k)$$

gives

$$f(s\,|\,P_j(k-1+\delta),\alpha) = (1-T(s))f(s\,|\,P_j(k-1),\alpha)/(1-\lambda_{j\alpha}(k)).$$

Let $\{s\,|\,P_k(k-1+\delta),\alpha\}$ represent the tumor size in among patients with doubling time α in the kth preclinical state immediately following screening at the start of year k and $\{s\,|\,I_k(k),\alpha\}$ represent the tumor size among patients with doubling time α in the kth interval state at the end of year k. Assuming that tumor volume grows exponentially from year $k-1+\delta$ to year k (approximately a 1-year period), then $\{s\,|\,I_k(k),\alpha\} = \beta_1(\alpha)\{s\,|\,P_k(k-1+\delta),\alpha\}$ where $\beta_1(\alpha) = \exp(\ln 2/(3\alpha))$. Since the distribution of $\{s\,|\,P_k(k-1+\delta),\alpha\}$ is $f_s(s\,|\,P_k(k-1+\delta),\alpha)$, then the distribution of $\{s\,|\,I_k(k),\alpha\}$ is $1/\beta_1(\alpha)f_s(s/\beta_1(\alpha)\,|\,P_k(k-1+\delta),\alpha)$.1-

A.6. Derivation of Eq. (23)

$$
\begin{aligned}
\varphi(\alpha\,|\,I_j(k)) &= \varphi(\alpha\,|\,I_j(k),P_j(k-1))\\
&= \varphi(\alpha,I_j(k)\,|\,P_j(k-1))/\mathrm{Prob}[I_j(k)\,|\,P_j(k-1)]\\
&= \varphi(\alpha\,|\,I_j(k-1))\mathrm{Prob}[I_j(k)\,|\,P_j(k-1),\alpha]/\mathrm{Prob}[I_j(k)\,|\,P_j(k-1)].
\end{aligned}
$$

Substituting

$$\mathrm{Prob}[I_j(k)\,|\,P_j(k-1),\alpha] = (1-\lambda_{j\alpha}(k))\boldsymbol{I}(j=k)$$

and

$$\mathrm{Prob}[I_j(k)\,|\,P_j(k-1)] = (1-\lambda_j(k))\boldsymbol{I}(j=k),$$

gives

$$\varphi(\alpha \mid I_j(k)) = (1 - \lambda_{j\alpha}(k))/(1 - \lambda_j(k))\varphi(\alpha \mid P_j(k-1))\boldsymbol{I}(j = k).$$

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