

# Models for the Effectiveness of Breast Cancer Screening

by

Natalia V. Iliouchina

Submitted to the Department of Electrical Engineering and Computer Science  
in Partial Fulfillment of the Requirements for the Degrees of  
Bachelor of Science in Electrical Engineering and Computer Science  
and Master of Engineering in Electrical Engineering and Computer Science  
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Author .....

Department of Electrical Engineering and Computer Science

May 23, 2001

Certified by ..... 5/23/2001 .....

John L. Wyatt

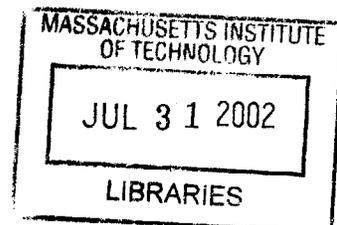
Thesis Supervisor

Accepted by .....

Arthur C. Smith

Chairman, Department Committee on Graduate Theses

**BARKER**



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## **ABSTRACT**

The choice of the recommended interval between consecutive mammographic screenings for different groups of women in the population is an important problem that significantly affects the breast cancer survival rate. This thesis addresses the problem of optimizing the interval between consecutive mammographic screenings in order to detect cancerous breast tumors before metastasis. It presents a number of increasingly complicated and realistic models that demonstrate the quantitative trade-off between the benefit, defined as the reduction in the number of patients with metastasis per year in the population of a fixed size, and cost, defined as the number of mammographic examination per year in the population of the same size. The results of this thesis are applicable to any screened type of cancer and can be used by public health policymakers in arriving at the recommendation for the interscreening interval for different groups of patients in the population.

Thesis Supervisor: John L. Wyatt

Title: Professor, Department of Electrical Engineering and Computer Science

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# I Introduction

The choice of the recommended interval between consecutive mammographic screenings for different groups of women in the population is an important problem that significantly affects the breast cancer survival rate. There is ample evidence that breast cancer death rate can be reduced by finding the tumors at smaller sizes, and mammographic screening has been shown to be capable of finding breast cancers at smaller sizes [1, 2]. Currently, the recommended interval varies significantly across countries and across different age groups, and there has been no comprehensive study that these recommendations are based upon.

There exist extensive data giving insight into the laws of tumor occurrence, growth, and probabilities of metastasis at different stages of tumor development [2, 3, 4]. From these data we can conclude that tumors occur unpredictably. However, the data suggest that the likelihood of cancerous breast tumor occurrence increases with age and hereditary predisposition, and differs across different ethnic groups. Once tumors arise, they grow at a predictable rate, and the likelihood of metastasis monotonically increases with the tumor size. Local or global metastasis is possible. Curing globally metastasized cancer by surgery or successfully treating it by other methods is almost always impossible, and therefore such cancer is fatal. Locally metastasized tumors can sometimes be removed by surgery, but the likelihood that not all the cancerous cells will be successfully removed is significantly higher than it is in the case of nonmetastasized tumors. The remaining cancerous cells are likely to give rise to new cancerous tumors, which can later result in global metastasis.

The data suggest that the likelihood of tumor detection by mammography monotonically increases with the tumor size. Intuitively it is clear that more frequent screening makes tumor metastasis before detection less likely. However, even infinitely frequent screening would not completely eliminate metastasis before detection. We are facing the need to quantify all this knowledge using both the empirical data and stochastic modeling. The goal of this research is to quantify and demonstrate the trade-off between the benefit and the cost corresponding to each choice of the interval between consecutive mammographic screenings. Benefit is defined as the reduction in the number of patients with global metastasis per year. Cost is defined as the number of mammographic exams per year. The quantitative findings of this research can be used by the public health policymakers in arriving at the recommendation for the interexamination interval for different groups of women in the population.

We are not aware of any methods that have been developed in this area, and are doing all the derivations from scratch, relying on the theory presented in Gallager's book [7, Ch. 2] and on the unpublished data provided by Jim Michaelson, M.D. [1, 2, 3, 4, 5, 6]. These data originate from the database maintained at the Massachusetts General Hospital and have been collected for over 20 years.

We approach this research by making a series of increasingly complicated and realistic models. We start by developing a basic, overly coarse model that builds upon the principal ideas of the tumor occurrence law, the tumor growth law, the probability of metastasis, the probability of detection by screening, and other relevant facts. In this basic model we make several simplifying assumptions that allow us to gain mathematical intuition, at the cost of making the model unrealistic in several aspects. We proceed by adding more realistic detail to the model in several steps, attempting to keep all of the previous intuition. We use each of the models to predict the relation between benefit (the reduction in the number of patients with global metastasis per year) and the cost (the number of examinations across the population in a year) for each value of the interscreening interval ranging from 1 to 6000 days. For each model we calculate *the probability of no metastasis before detection*, *the benefit*, *the cost*, *the ratio of benefit to cost*, and *the marginal benefit per unit cost* as functions of the interscreening interval.

Section 2 describes the structure of the model in detail, Section 3 outlines the basic assumptions behind the simplest model M0, Section 4 lists possible ways of making the model more realistic in the order of their perceived relevance, Section 5 analyzes the model M0, and the subsequent sections describe and analyze each of the increasingly complex and realistic models. Section 13 lists the notation used throughout the thesis.

## II Structure of the Model

Each model is described by the following laws and quantities: tumor incidence law, tumor growth law, probability of metastasis, probability of detection by mammography, probability of detection by self-examination, the screening interval, the delay between the tumor detection and the tumor removal, and the probability of an incomplete removal.

- a) **Tumor incidence.** In each model we assume that tumors arise as a Poisson process in each woman in the population independently. In a realistic model  $\lambda$  is sufficiently small that the probability of more than 1 new tumor arising in an interexamination period is negligible.

We do not count tumors that arise from metastasis in this thesis. That is, in the model  $\lambda$  represents the rate of arrival of tumors emerging from normal cells only, and does not include the arrivals of new tumors caused by metastasis of other tumors already present in the body. In all the models described in this thesis metastasis means global metastasis. Since global metastasis is nearly always fatal while local metastasis is likely to be curable, we approximate death by global metastasis and ignore the possibility of local metastasis. Later in this research we might attempt to quantify local metastasis and assign a nonzero probability to the curability of global metastasis.

In the models throughout this thesis  $\lambda$  is a constant, that is the rate of tumor arrivals is constant in time in each woman. We also take  $\lambda$  to be equal across all women in the population. Later in the research, we plan to create more realistic models that will require a distribution of  $\lambda$ 's across population to account for different groups in the population having a different risk of cancerous tumor incidence. Whichever the distribution of  $\lambda$  across population, the net increase in the number of tumors in the population over time will remain Poisson, since the sum of independent Poisson processes is Poisson. More realistic models will also require that we include the increase of tumor incidence with age in each woman independently ( $\lambda \rightarrow \lambda(t)$ ). We expect that this modification will leave most of our reasoning unchanged, since an inhomogenous Poisson process retains many of the simple properties of a homogenous Poisson process.

- b) **Tumor growth law.** We measure tumors by the number of cells,  $n(t)$ , and define a tumor as coming into existence when it attains a minimal size  $n_m$ . All the physically meaningful results must be independent of the particular value of  $n_m$ , provided it is chosen sufficiently small that the likelihood of metastasis and of detection are both zero or negligible for tumors of size less than  $n_m$ . Throughout this thesis, we take the tumor growth law in the form of a differential equation

$$\frac{dn}{dt} = f(n), \quad (1)$$

where  $n(t)$  is modeled as continuous.

We take  $f(n) = rn$ , and therefore the differential equation takes the form

$$\frac{dn}{dt} = rn \quad (2)$$

with solution

$$n(t) = n_m e^{rt} \quad (3)$$

where the tumor has attained the minimal size  $n_m$ , i.e., “came into existence” at  $t=0$ .

Later in the research we may consider more complex growth laws, e.g. the logistic equation.

- c) **Probability of metastasis.** The literature shows that the probability that a tumor has metastasized is an increasing function of its present size. To make the algebra less awkward, we work in terms of probability of no metastasis to date for a tumor of  $n$  cells, which we define as

$$h(n) = Pr \{a \text{ tumor of } n \text{ cells has not yet metastasized}\} \quad (4)$$

- d) **Probability of detection by mammography.** We model the probability of detection of a

tumor by a screening procedure as a function of the size of the tumor.

$$P_{d,mamm}(n) = Pr \{a \text{ tumor of } n \text{ cells is detected at a single exam}\} \quad (5)$$

- e) **Probability of detection by self-examination.** We model the probability of detection of a tumor by self-examination as a function of the size of the tumor.

$$P_{d,self}(n) = Pr \{a \text{ tumor of } n \text{ cells is detected by self - examination}\} \quad (6)$$

Throughout this thesis, we assume that self-examination is continuous, i.e. occurs at every instant. Later we expect to create more realistic models which will represent self-examination as happening at discrete time intervals, significantly smaller than the screening interval.

If  $n_{d,mamm}$  is the minimal size of the tumor detectable by mammography, and  $n_{d,self}$  is the minimal size of the tumor detectable by self-examination, we always assume  $n_{d,mamm} \leq n_{d,self}$ .

- f) **Screening interval.** The interval between screening examinations  $T$  is the key component in the model. We begin the analysis of each model by finding

$$P(T) = Pr \{no \text{ metastasis before detection for screening interval } T\} \quad (7)$$

We proceed by finding the reduction in the number of patients with global metastasis per year  $B(T)$ , the reduction in the number of patients with metastasis per individual exam  $\frac{B(T)}{C(T)}$ , and the expected increase in the reduction of the number of patients with metastasis per additional examination  $\frac{\partial B}{\partial C}$ , as functions of  $T$ .

Throuout this thesis we take  $T$  to be constant across time and population. Later we plan to create more realistic models that assume  $T$  to be a random variable representing the distribution of screening intervals both in time and in population, with known expected value and variance.

- g) **Delay between tumor detection and tumor removal.** Under realistic conditions, there always exists a delay between the time when a tumor is detected and the time when it is removed.

Throught this thesis we assume that this delay  $d$  is zero, that is, the tumor is taken out the moment it is detected, whether by mammography or by self-examination. Later in the research we will relax this assumption and take  $d$  to be a positive constant or a distribution with known expectation and variance.

- h) **Probability of an incomplete removal.** Under realistic conditions, it is possible that not all the tumor cells get removed in surgery. If the surgeon misses part of the tumor, the tumor

will continue to grow from the remaining size after the surgery.

$$P_{incomplete} = Pr \{ \text{part of the tumor is missed at the surgery} \} \quad (8)$$

Throughout this thesis we take  $P_{incomplete} = 0$ . Later in the research we take  $0 < P_{incomplete} \ll 1$ .

- i) **Roles of radiation and chemotherapy.** We ignore the roles of both radiation and chemotherapy and do not attempt to quantify them in our models.
- j) **Changes in population size.** The population of women of a given age at risk decreases with age due to deaths from all causes. In this thesis we ignore this fact and simply consider a population of fixed size over time.
- k) **Definition of cost.** In all models we define cost as the number of exams per year. Cost is proportionate to the number of women in the population  $w$ , and inversely proportionate to the interscreening interval  $T$ . We denote cost by  $C(T)$ .

$$C(T) = \frac{w}{T} \quad (9)$$

- l) **Definition of benefit.** In all models we define benefit as the difference between the expected number of patients with one or more metastasized tumors per year in the absence of screenings, and the expected number of patients with one or more metastasized tumors per year in the presence of screenings. In other words, benefit signifies the reduction in the number of patients with metastasis per year in population of size  $w$ . We denote benefit by  $B(T)$ .

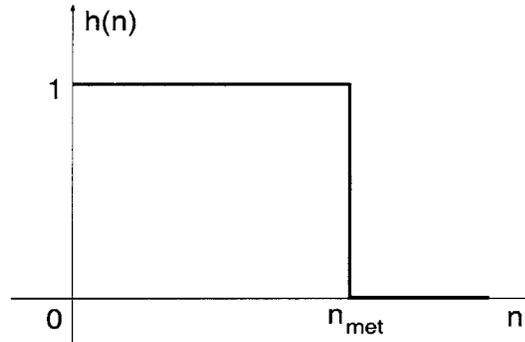
$$B(T) = E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis in 1 year} \\ \text{with no screening} \end{array} \right\} - E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis in 1 year} \\ \text{with screening} \end{array} \right\} \quad (10)$$

### III Description of the simplest model M0

Each of the models that we create consists of the twelve parts described in the previous section. We start by completely defining the simplest model in terms of the quantities and laws above and try to derive and analyze all the relevant quantities and laws based on our definitions. We call our simplest model M0. This model is overly coarse, and its results cannot be viewed as realistic. This model, however, builds upon two very important facts about tumors : Poisson occurrence and exponential growth. Subsequently we will add more realistic detail to the model in several steps.

- a) Tumor incidence is modeled as a homogenous Poisson process with rate  $\lambda$ , constant in time and across the population.
- b) Tumor growth law is modeled by  $n(t) = n_m e^{rt}$ . In this model we only use the growth law to find the time intervals  $t_{d,mamm}$ ,  $t_{d,self}$ , and  $t_{met}$ : the time it takes the tumor to grow to the size detectable by mammography, the size detectable by self-examination, and the size at which it metastasizes, respectively.
- c) Probability of no metastasis to date, is modeled as a step function of  $n$ , where  $n_{met}$  is the metastasis threshold:

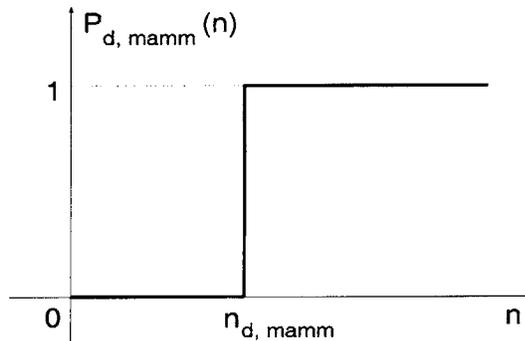
$$h(n) = \begin{cases} 0, & n \geq n_{met} \\ 1, & n < n_{met} \end{cases} \quad (11)$$



From the tumor growth law we can derive  $t_{met}$ , the time it takes a tumor to grow from size  $n_m$  to size  $n_{met}$ .

- d) Probability of detection by mammography is modeled as a step function of  $n$ , where  $n_{d,mamm}$  is the detection threshold:

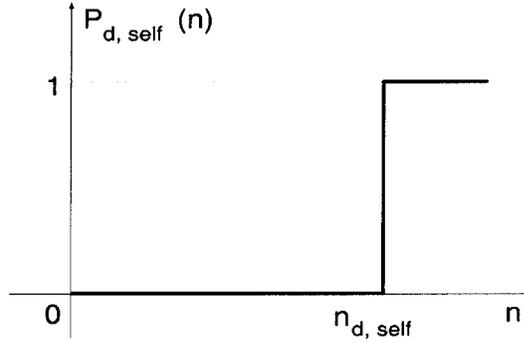
$$P_{d,mamm}(n) = \begin{cases} 1, & n \geq n_{d,mamm} \\ 0, & n < n_{d,mamm} \end{cases} \quad (12)$$



Again, from the tumor growth law we can derive  $t_{d,mamm}$ , the time it takes a tumor to grow from size  $n_m$  to size  $n_{d,mamm}$ .

- e) Probability of detection by self-examination is modeled as a step function of  $n$ , where  $n_{d,self}$  is the threshold for detection by self-examination:

$$P_{d,self}(n) = \begin{cases} 1, & n \geq n_{d,self} \\ 0, & n < n_{d,self} \end{cases} \quad (13)$$



Again, from the tumor growth law, we can derive  $t_{d,self}$ , the time it takes a tumor to grow from size  $n_m$  to size  $n_{d,self}$ . We assume that self-examination is performed continuously, i.e. it occurs at every instant.

- f) We take the screening interval to be constant in time and across population. We denote the screening interval as  $T$ .
- g) We assume that there is no delay between tumor detection and surgery, that is  $d = 0$ .
- h) We assign zero probability to an event that the surgeon misses part of the tumor during the surgery, that is  $P_{incomplete} = 0$ .
- i) We ignore the roles of radiation and chemotherapy.
- j) We ignore the changes in the population size.
- k) We define cost as

$$C(T) = \frac{w}{T} \quad (14)$$

- l) We define benefit as

$$B(T) = E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis in 1 year} \\ \text{with no screening} \end{array} \right\} - E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis in 1 year} \\ \text{with screening} \end{array} \right\} \quad (15)$$

In this model we make an assumption that  $t_{d,mamm} < t_{met}$ , since if it were not the case, any examinations would be pointless because they would have no chance to detect a tumor before metastasis, and therefore reduce the number of patients with metastasis in the population.

There are two possible cases describing the relation between  $t_{d,self}$  and  $t_{met}$ . In the first case  $t_{d,self} < t_{met}$ , and therefore, each tumor is detected and removed before metastasis, since self-examination is continuous and there is no delay between detection and surgery. In this case mammography is useless, since self-examination saves all the lives by itself. In the second case  $t_{d,self} \geq t_{met}$ , and therefore no tumor is detected by self-examination before metastasis. In this case self-examination is useless, since it will detect no tumor before metastasis, and will save no lives. Since we are interested in finding out the relation between the interscreening interval  $T$  and the probability of no metastasis before detection, in this model we will focus only on the second case.

In summary, we assume in model M0 that  $t_{d,mamm} < t_{met} \leq t_{d,self}$ .

## IV Making the model more realistic

The model described above is imperfect and unrealistic in several ways. In this section we describe useful alterations to the model, and later modify the model one step at a time while keeping all the previous modifications without loss of intuition. Of these proposed alterations, only the first three are described and analyzed in this thesis. We hope to make the remaining five alterations, as well as any other that might come up, further in this research.

- 1) Represent the probability of no metastasis to date as a continuous function of tumor size.
- 2) Represent the probability of detection by mammography as a continuous function of tumor size.
- 3) Represent the probability of detection by self-examination as a continuous function of tumor size
- 4) Represent the interexamination time as a distribution, rather than a constant, both across time and across population.
- 5) Introduce a delay between tumor detection and surgery. In the simpler version of the model the delay can be represented as a constant, while in the more realistic version it should be represented as a distribution.
- 6) Relax the assumption that self-examination is performed continuously. In the simpler version of the modified model we can assume that it is performed at frequent constant intervals. In the more realistic version, we should represent the intervals between self-examinations as a distribution.

- 7) Relax the assumption that surgery renders a tumor completely harmless. Introduce a non-zero probability that a part of the tumor is missed at the surgery and the tumor continues to grow from the size it is left at, risking metastasis in the future.
- 8) Relax the assumption that the population size remains constant.

## V Analysis of M0

We now perform a detailed analysis of the model M0 described in Section II, and calculate the probability of no metastasis before detection, the benefit, the benefit per unit cost, and the marginal benefit per unit cost corresponding to this model. We start with calculating several useful quantities that do not directly enter the calculation of  $P(T)$ ,  $B(T)$ ,  $\frac{B(T)}{C(T)}$  or  $\frac{\partial B}{\partial C}$ , but provide a helpful insight and can be useful later in the research.

- a) First, we calculate the probability  $p_b$  that a woman has, right before a particular exam, one or more previously undetected tumors, all of size  $\geq n_m$ . Let  $t_1$  be the time of the exam in question. If the woman has one or more previously undetected tumors of size  $n_m$  or bigger, it means that they “came into existence” (i.e. existed and had size  $n_m$ ) in the time interval  $(t_1 - (t_{d,mamm} + T), t_1)$ . This result follows from the fact that those tumors would have to “have come into existence” before the time of the exam in question  $t_1$ , but would have to come into existence at a time that was too late to have them detectable at the previous examination. Therefore, at the previous examination at time  $t_1 - T$ , all the tumors would have to be “younger” than  $t_{d,mamm}$ , and therefore they all would have to “come into existence” no earlier than  $t_1 - (t_{d,mamm} + T)$ .

For a Poisson process the probability of no tumor arising in that time interval is

$$e^{-\lambda(T+t_{d,mamm})} \frac{[\lambda(T+t_{d,mamm})]^0}{0!},$$

and therefore it follows that the probability of one or more tumors arising in that time interval is

$$1 - e^{-\lambda(T+t_{d,mamm})} \frac{[\lambda(T+t_{d,mamm})]^0}{0!} = 1 - e^{-\lambda(T+t_{d,mamm})}$$

Since in reality a tumor is relatively unlikely, and therefore  $p_b \ll 1$  (and, equivalently,  $\lambda(T+t_{d,mamm}) \ll 1$ ), we can approximate the above quantity by  $\lambda(T+t_{d,mamm})$ .

$$p_b = 1 - e^{-\lambda(T+t_{d,mamm})} \approx \lambda(T+t_{d,mamm}) \quad (16)$$

b) Now we calculate the probability  $p_a$  that a woman has, right after a particular exam, one or more tumors. This expression should be smaller than the one above, since in this model we assume that a tumor is removed at the very moment it is detected, and therefore  $p_a$  should be affected by the probability that a tumor is removed at a particular exam. Therefore, we are looking at the probability that one or more tumors “came into existence” in the time interval  $(t_1 - t_{d,mamm}, t_1]$ , i.e. that there was one or more tumors not detectable at the exam at the time  $t_1$ . Similarly to  $p_b$ , we can derive that  $p_a = 1 - e^{-\lambda t_{d,mamm}}$ , and since a tumor is relatively unlikely, and  $\lambda t_{d,mamm} \ll 1$ , we can approximate  $p_a$  by  $\lambda t_{d,mamm}$ .

$$p_a = 1 - e^{-\lambda t_{d,mamm}} \approx \lambda t_{d,mamm} \quad (17)$$

c) Next we define  $P_{de}$  to be the conditional probability that one or more tumors are detected on an exam, given that one or more previously undetected tumors are present.

$$P_{de} = Pr \left\{ \begin{array}{l} 1 \text{ or more tumors} \\ \text{detected} \end{array} \middle| \begin{array}{l} 1 \text{ or more previously} \\ \text{undetected tumors present} \end{array} \right\}$$

$$1 - P_{de} = Pr \left\{ \begin{array}{l} \text{no tumor} \\ \text{detected} \end{array} \middle| \begin{array}{l} \text{one or more previously} \\ \text{undetected tumors present} \end{array} \right\} \quad (18)$$

If A and B are disjoint,  $Pr \{C | A \cup B\} = \frac{Pr\{C \cap A\} + Pr\{C \cap B\}}{Pr\{A\} + Pr\{B\}}$ . From this law it follows that

$$1 - P_{de} = \frac{\sum_{k=1}^{\infty} Pr \{ \text{no tumor found and } k \text{ tumors present} \}}{\sum_{m=1}^{\infty} Pr \{ m \text{ tumors present} \}} =$$

$$\frac{\sum_{k=1}^{\infty} Pr \{ \text{no tumor found} | k \text{ tumors present} \} \cdot Pr \{ k \text{ tumors present} \}}{\sum_{m=1}^{\infty} Pr \{ m \text{ tumors present} \}} \quad (19)$$

The event that m previously undetected tumors are present at a particular exam is equivalent to m tumors having originated in the time period  $(t_1 - (t_{d,mamm} + T), t_1]$ , as discussed in part a of this section. Therefore, from the properties of Poisson processes, this probability is equal

to

$$e^{-\lambda(T+t_{d,mamm})} \frac{[\lambda(T+t_{d,mamm})]^m}{m!}.$$

Also, from the properties of Poisson processes we know that if  $k$  previously undetected tumors are present, the the times their sizes pass through  $n_m$  (and therefore those tumors “come to existence”) are uniformly distributed in  $(t_1 - (T+t_{d,mamm}), t_1]$  and conditionally independent. Given that they all pass through size  $n_m$  in this interval,

$$\begin{aligned} Pr \left\{ \begin{array}{l|l} \text{no tumor} & k \text{ tumors} \\ \text{found} & \text{present} \end{array} \right\} &= Pr \left\{ \begin{array}{l|l} \text{all } k \text{ tumors} & k \text{ tumors} \\ \text{initiated within} & \text{initiated within} \\ (t_1 - t_{d,mamm}, t_1] & (t_1 - (T + t_{d,mamm}), t_1] \end{array} \right\} \\ &= \left( \frac{t_{d,mamm}}{t_{d,mamm} + T} \right)^k \end{aligned} \quad (20)$$

Bringing all the expressions together yields

$$\begin{aligned} 1 - P_{de} &= \frac{\sum_{k=1}^{\infty} \left( \frac{t_{d,mamm}}{t_{d,mamm} + T} \right)^k e^{-\lambda(T+t_{d,mamm})} \frac{[\lambda(T+t_{d,mamm})]^k}{k!}}{\sum_{m=1}^{\infty} e^{-\lambda(T+t_{d,mamm})} \frac{\lambda^m (T+t_{d,mamm})^m}{m!}} \\ &= \frac{e^{\lambda t_{d,mamm}} - 1}{e^{\lambda(T+t_{d,mamm})} - 1} \end{aligned} \quad (21)$$

From this expression, we establish that

$$\begin{aligned} P_{de} &= 1 - \frac{e^{\lambda t_{d,mamm}} - 1}{e^{\lambda(T+t_{d,mamm})} - 1} = \frac{e^{\lambda(T+t_{d,mamm})} - e^{\lambda t_{d,mamm}}}{e^{\lambda(T+t_{d,mamm})} - 1} \\ &\approx \frac{T}{T + t_{d,mamm}}, \end{aligned} \quad (22)$$

where the latter approximation holds, if  $p_b \ll 1$ .

d) We now turn to deriving the long term average number of tumors detected per year, i.e.

$$\lim_{t \rightarrow \infty} \frac{E\{\text{number of tumors detected in } [0, t]\}}{t},$$

where  $t$  is measured in years.

Intuitively we can arrive at the value of the above limit as follows. Each woman produces tumors at the rate  $\lambda$ , and there are  $w$  women in the population. Each tumor is detected at

most  $T + t_{d,mamm}$  years after it “comes into existence,” whether or not it has metastasized by then. Since we ignore the changes in the size of population due to deaths from tumor metastasis, we can state that the expected number of tumors detected per year is  $\lambda w$ .

- e) Now let’s look at the long term average number of exams per year that detect one or more tumors. Intuitively, this number should be just slightly smaller than  $\lambda w$ , the number above, since the probability of two or more tumors developing in the same woman simultaneously is small, and most exams will detect at most one tumor. Denote the number of exams per year that detect one or more tumors by  $N_{de}$ . It is quite obvious that  $E\{N_{de}\} = N \cdot P_{de} \cdot p_b$ , where  $N$  is the total number of exams per year. From this statement we infer that

$$\begin{aligned}
E\{N_{de}\} &= \frac{w}{T} \cdot P_{de} \cdot p_b \\
&= \frac{w}{T} \cdot \frac{e^{\lambda(T+t_{d,mamm})} - e^{\lambda t_{d,mamm}}}{e^{\lambda(T+t_{d,mamm})} - 1} \cdot (1 - e^{-\lambda(T+t_{d,mamm})}) \\
&= \frac{w}{T} \cdot e^{\lambda t_{d,mamm}} (e^{\lambda T} - 1) \cdot e^{-\lambda(T+t_{d,mamm})} \frac{e^{\lambda(T+t_{d,mamm})} - 1}{e^{\lambda(T+t_{d,mamm})} - 1} \\
&= \frac{w}{T} (1 - e^{-\lambda T}) \approx \lambda w
\end{aligned} \tag{23}$$

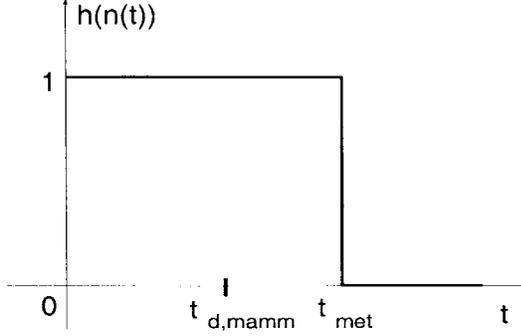
As previously noted, this number is just slightly smaller than  $\lambda w$ , the number of tumors detected per year. If  $\lambda T \ll 1$ , which makes it extremely unlikely that a woman would develop two independent tumors in a single interexamination interval, these numbers are approximately equal.

- f) Now we derive  $P(T) = Pr \left\{ \begin{array}{l} \text{a single tumor is detected before it} \\ \text{metastasizes for screening interval } T \end{array} \right\}$ . If we let  $T$  represent the interexamination interval in days,

$$\begin{aligned}
P(T) &= \sum_{k=0}^{T-1} Pr \left\{ \begin{array}{l} \text{detection occurs} \\ \text{before} \\ \text{metastasis} \end{array} \left| \begin{array}{l} \text{tumor size} \\ \text{passed detection} \\ \text{threshold } k \text{ days} \\ \text{before screening} \end{array} \right. \right\} \cdot Pr \left\{ \begin{array}{l} \text{tumor size} \\ \text{passed threshold} \\ k \text{ days before} \\ \text{screening} \end{array} \right\} \\
&= \sum_{k=0}^{T-1} Pr \left\{ \begin{array}{l} \text{detection occurs} \\ \text{before} \\ \text{metastasis} \end{array} \left| \begin{array}{l} \text{tumor size passed} \\ \text{threshold } k \text{ days} \\ \text{before screening} \end{array} \right. \right\} \cdot \frac{1}{T}
\end{aligned} \tag{24}$$

Equation (11) is a simple model for the probability a tumor has not yet metastasized as a function of  $n$ , the tumor size. Letting  $t$  represent the tumor age,

$$h(n(t)) = \begin{cases} 0, & t \geq t_{met} \\ 1, & t < t_{met} \end{cases} \quad (25)$$

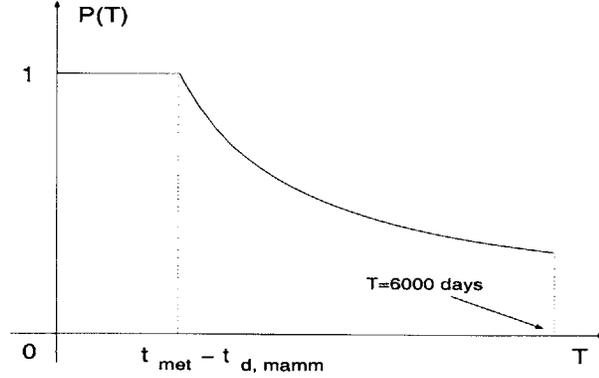


$$\begin{aligned}
P(T) &= \sum_{k=0}^{T-1} Pr \left\{ \begin{array}{l} \text{detection occurs} \\ \text{before metastasis} \end{array} \left| \begin{array}{l} \text{tumor size passed} \\ \text{detection threshold } k \text{ days} \\ \text{before screening} \end{array} \right. \right\} \cdot \frac{1}{T} \\
&= \sum_{k=0}^{T-1} Pr \left\{ \begin{array}{l} \text{detection occurs} \\ \text{before} \\ \text{metastasis} \end{array} \left| \begin{array}{l} t_b = t_e - t_{d,mamm} - k \end{array} \right. \right\} \cdot \frac{1}{T} \\
&= \sum_{k=0}^{T-1} Pr \left\{ \begin{array}{l} \text{detection occurs} \\ \text{before} \\ \text{metastasis} \end{array} \left| \begin{array}{l} \text{tumor age} \\ \text{at } t_e = t_{d,mamm} + k \end{array} \right. \right\} \cdot \frac{1}{T} \\
&\approx \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(t) dt \\
&= \begin{cases} 1, & T \leq t_{met} - t_{d,mamm} \\ \frac{t_{met} - t_{d,mamm}}{T}, & T > t_{met} - t_{d,mamm} \end{cases} \quad (26)
\end{aligned}$$

g) We now turn to the benefit calculation. As described in Section II, we will measure benefit as the difference between the expected number of patients with one or more metastasized tumors per year in the absence of screenings, and the expected number of patients with one or more metastasized tumors per year in the presence of screenings.

There are two separate cases to be considered in determining the expectation of the number of usefully detected tumors at any given examination.

i)  $t_{met} > t_{d,mamm} + T$ . In this case, it is certain that no tumors metastasize before detection,

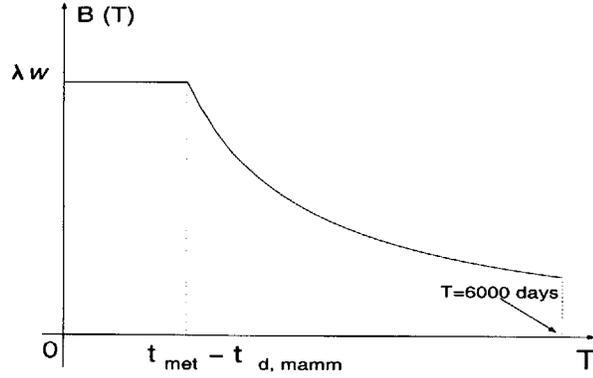


and therefore the expected number of tumors detected in a metastasis free patient at a given examination is just the expected number of tumors detected at a given examination,  $\lambda T$ .

- ii)  $t_{met} \leq t_{d,mamm} + T$ . In this case, some tumors will be missed at an examination at time  $t_1$  and will have already metastasized at the examination at time  $t_2 = t_1 + T$ . Intuitively, the expected number of tumors found in a metastasis free patient at a given examination is smaller in this case than it is if  $t_{met} > t_{d,mamm} + T$ .

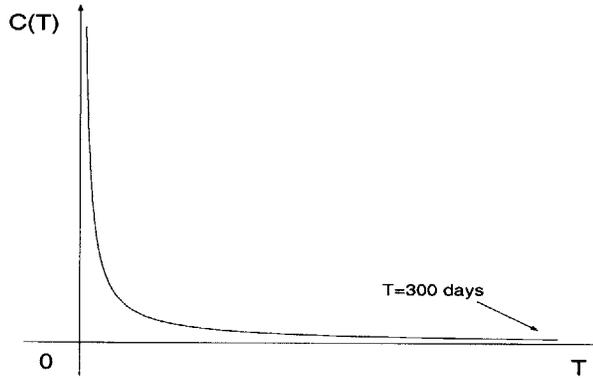
$$\begin{aligned}
B(T) &= E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis} \\ \text{in 1 year} \\ \text{with no screening} \end{array} \right\} - E \left\{ \begin{array}{l} \text{number of women} \\ \text{with } \geq 1 \text{ metastasis} \\ \text{in 1 year} \\ \text{with screening} \end{array} \right\} \\
&= w \cdot \left[ Pr \left\{ \begin{array}{l} \geq 1 \text{ tumor would} \\ \text{metastasize in 1 year} \\ \text{in 1 woman} \\ \text{with no screening} \end{array} \right\} - Pr \left\{ \begin{array}{l} \geq 1 \text{ tumor would} \\ \text{metastasize in 1 year} \\ \text{in 1 woman} \\ \text{with screening} \end{array} \right\} \right] \\
&= w \cdot [1 - e^{-\lambda}] - w \cdot [1 - e^{-\lambda(1-P(T))}] \\
&= w \cdot [e^{-\lambda(1-P(T))} - e^{-\lambda}] = w e^{-\lambda} \cdot [e^{\lambda P(T)} - 1] \\
&= \begin{cases} w \cdot [1 - e^{-\lambda}], & T \leq t_{met} - t_{d,mamm} \\ w \cdot [e^{\frac{-\lambda(T-t_{met}+t_{d,mamm})}{T}} - e^{-\lambda}], & T > t_{met} - t_{d,mamm} \end{cases}
\end{aligned}$$

$$= \begin{cases} w e^{-\lambda} \cdot [e^{\lambda} - 1], & T \leq t_{met} - t_{d,mamm} \\ w e^{-\lambda} \cdot \left[ e^{\frac{\lambda(t_{met} - t_{d,mamm})}{T}} - 1 \right], & T > t_{met} - t_{d,mamm} \end{cases} \quad (27)$$



h) As described in Section II,

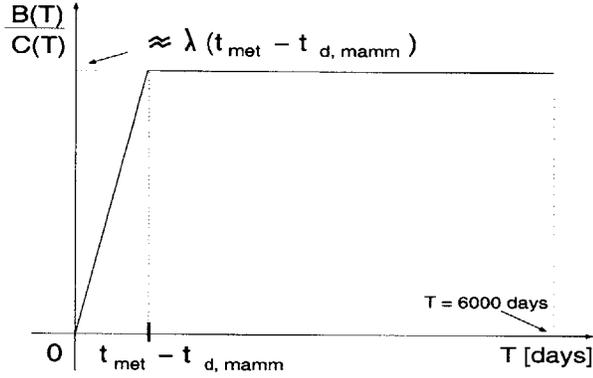
$$C(T) = \frac{w}{T} \quad (28)$$



i) We now derive the expression for the ratio of benefit to cost,  $\frac{B(T)}{C(T)}$ , which represents the reduction in the number of patients with global metastasis in population  $w$  per individual exam as a function of the screening interval.

$$\frac{B(T)}{C(T)} = T \cdot [e^{-\lambda(1-P(T))} - e^{-\lambda}] = T e^{-\lambda} \cdot [e^{(1-P(T))} - 1]$$

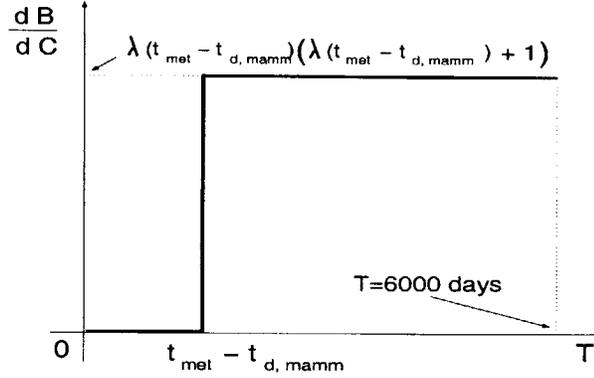
$$\begin{aligned}
&= \begin{cases} T \cdot [1 - e^{-\lambda}], & T \leq t_{met} - t_{d,mamm} \\ T \cdot \left[ e^{\frac{-\lambda \cdot (T - t_{met} + t_{d,mamm})}{T}} - e^{-\lambda} \right], & T > t_{met} - t_{d,mamm} \end{cases} \\
&= \begin{cases} T e^{-\lambda} \cdot [e^{\lambda} - 1], & T \leq t_{met} - t_{d,mamm} \\ T e^{-\lambda} \cdot \left[ e^{\frac{\lambda \cdot (t_{met} - t_{d,mamm})}{T}} - 1 \right], & T > t_{met} - t_{d,mamm} \end{cases} \quad (29)
\end{aligned}$$



j) Lastly, we derive the expression for marginal benefit per unit cost,  $\frac{\partial B}{\partial C}$ , as a function of the screening interval. Marginal benefit per unit cost represents the expected increase in the reduction of the number of patients with global metastasis in population  $w$  per additional examination per year.

$$\begin{aligned}
\frac{\partial B}{\partial C} &= \frac{-\frac{\partial B}{\partial T}}{-\frac{\partial C}{\partial T}} \\
&= \begin{cases} 0, & T < t_{met} - t_{d,mamm} \\ \frac{\frac{\lambda \cdot w}{T^2} \cdot (t_{met} - t_{d,mamm}) \cdot e^{\left[ \frac{-\lambda \cdot (T - t_{met} + t_{d,mamm})}{T} \right]}}{\frac{w}{T^2}}, & T \geq t_{met} - t_{d,mamm} \end{cases} \\
&= \begin{cases} 0, & T < t_{met} - t_{d,mamm} \\ \lambda \cdot (t_{met} - t_{d,mamm}) \cdot e^{\left[ \frac{-\lambda \cdot (T - t_{met} + t_{d,mamm})}{T} \right]}, & T \geq t_{met} - t_{d,mamm} \end{cases}
\end{aligned}$$

Both  $\frac{B(T)}{C(T)}$  and  $\frac{\partial B}{\partial C}(T)$  rise as  $T$  drops until  $T$  reaches the value of  $t_{met} - t_{d,mamm}$  and then fall as  $T$  is diminished beyond that. There is a value of  $T = t_{met} - t_{d,mamm}$  that uniquely maximizes both



$\frac{B(T)}{C(T)}$  and  $\frac{\partial B}{\partial C}(T)$  and that nonuniquely maximizes B, i.e. the largest value of T that is guaranteed to catch every tumor before metastasis. This feature is unique to M0, and does not hold in all more complex models.

Now we use the above derivations to produce graphs based on the data provided by Jim Michaelson [1, 2, 4, 6]. In this model we let  $n_{d, \text{mamm}}$  be the number of cells in a 7 mm diameter tumor, which is the size corresponding to the probability of detection by mammography of 50% [6, p.6]. We let  $n_{\text{met}}$  be the number of cells in a 35 mm diameter tumor, which is the size corresponding to the probability of metastasis of 50% [4, p.13]. We assume that cell density is equal to  $10^8 \text{ cells/cm}^3$  [4, p.2]. We take the doubling time of tumors to be 130 days [5], and use the exponential growth law. We take  $\lambda = \frac{1}{250} \text{ years}^{-1} = \frac{1}{91250} \text{ days}^{-1}$ . We assume that  $w = 1000$ . Based on these assumptions and on the fact that we take  $n_m$  be the number of cells in a tumor that is 1 mm in diameter, we have:

$$n(t) = n_m e^{rt} \quad (30)$$

$$r = 0.00533 \text{ days}^{-1} \quad (31)$$

$$n_m = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (0.05 \text{ cm})^3 = 52,333 \text{ cells} \quad (32)$$

$$n_{d, \text{mamm}} = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (0.35 \text{ cm})^3 = 17,950,333 \text{ cells} \quad (33)$$

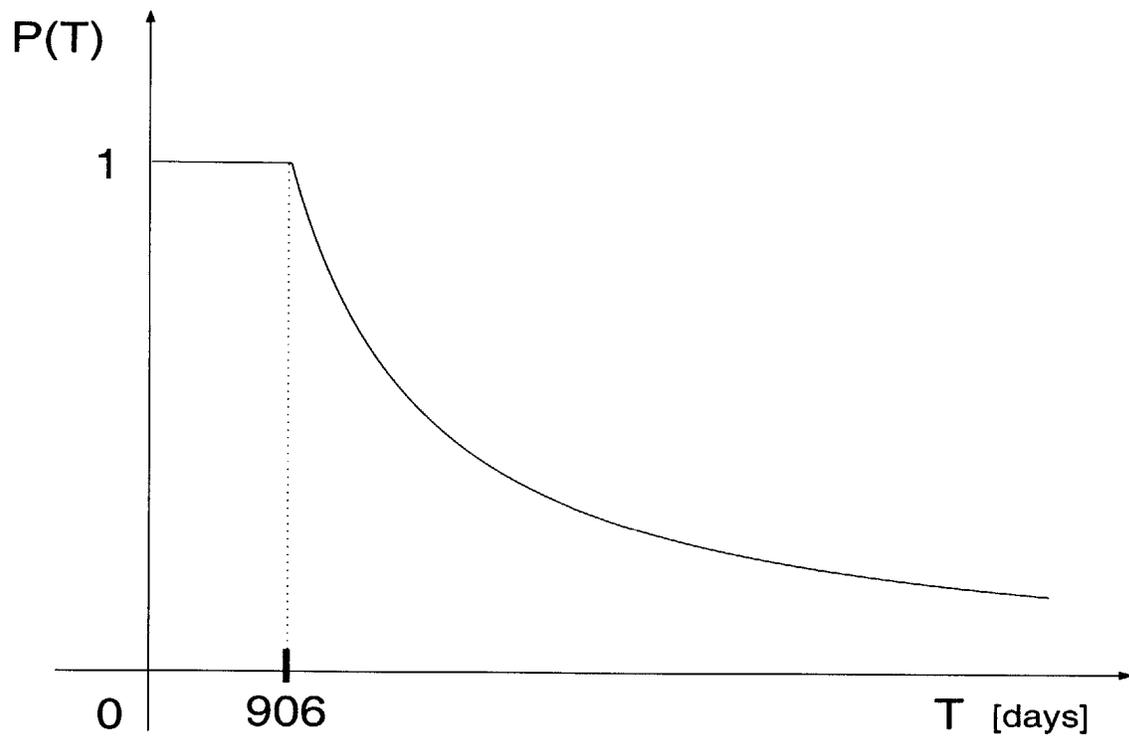
$$n_{\text{met}} = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (1.75 \text{ cm})^3 = 2,243,791,700 \text{ cells} \quad (34)$$

$$17,950,333 = 52,333 e^{0.00533 \cdot t_{d, \text{mamm}}}$$

$$t_{d, \text{mamm}} = 1095 \text{ days} \quad (35)$$

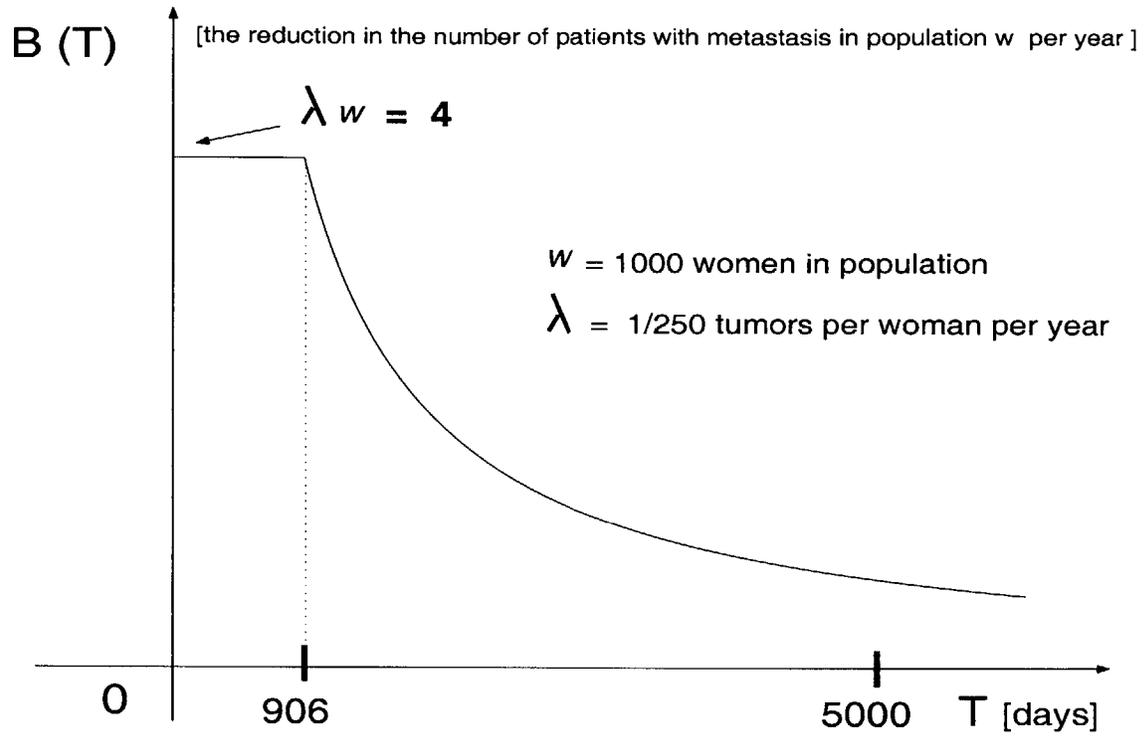
$$2,243,791,700 = 52,333 e^{0.00533 \cdot t_{\text{met}}}$$

$$t_{\text{met}} = 2001 \text{ days} \quad (36)$$



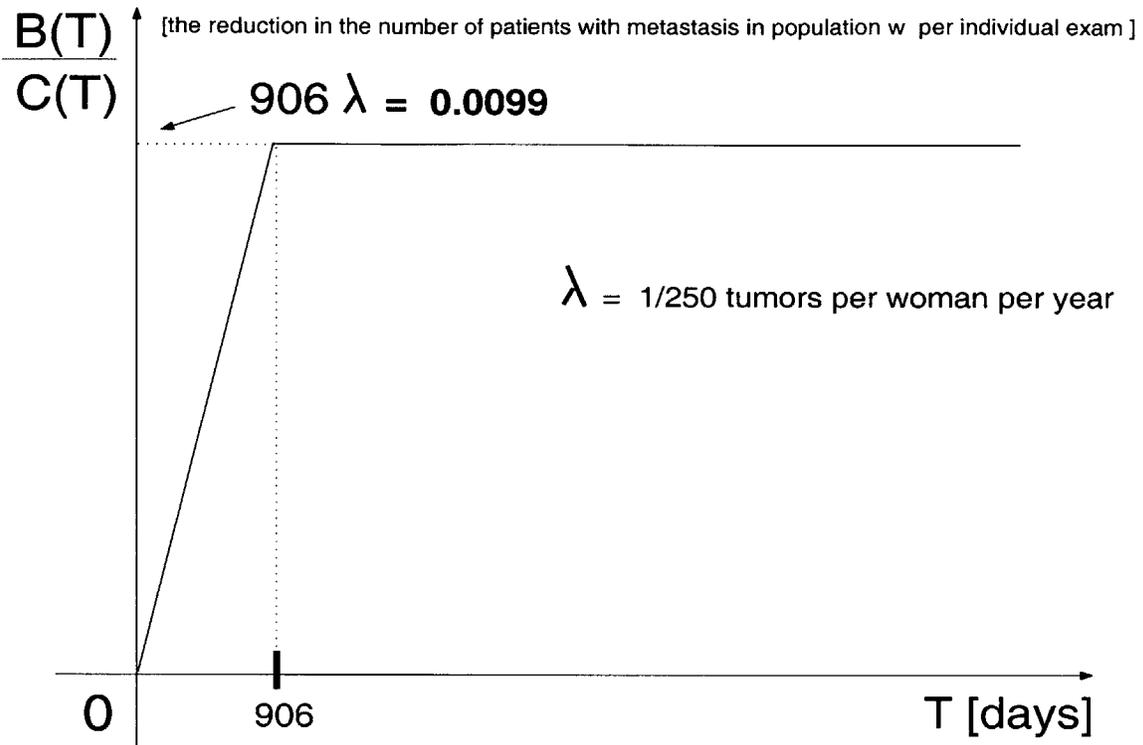
$$P(T) = \begin{cases} 1, & T \leq 906 \\ \frac{906}{T}, & T > 906 \end{cases} \quad (37)$$

$P(T)$  is the probability that a single tumor is detected before metastasis.



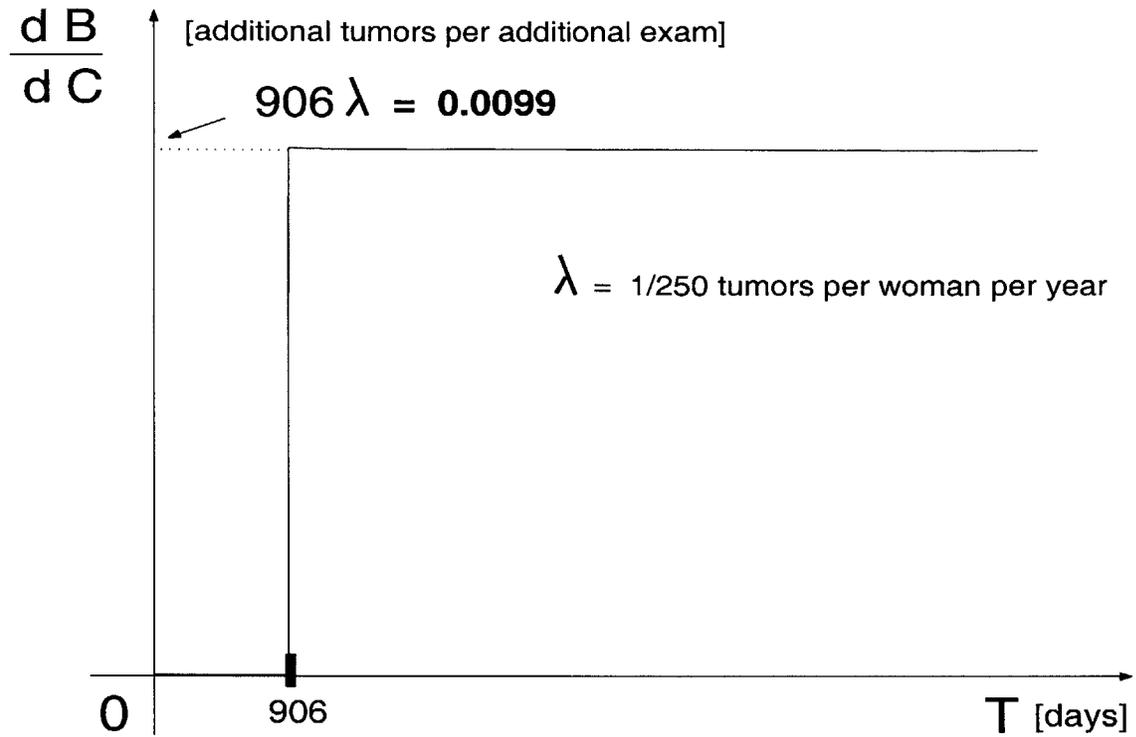
$$B(T) = \begin{cases} 1000 \cdot \left[1 - e^{-\frac{1}{250}}\right] \approx \lambda w = 4, & T \leq 906 \\ 1000 \cdot \left[e^{-\frac{1}{250} \cdot \frac{(T-906)}{T}} - e^{-\frac{1}{250}}\right] = 1000 e^{-\frac{1}{250}} \cdot \left[e^{\frac{906}{250 T}} - 1\right], & T > 906 \end{cases} \quad (38)$$

For an interexamination interval  $T \leq 906$  days, every tumor is detected prior to metastasis in this model.  $B(T)$  is the reduction in the number of patients with metastasis in population  $w$  per year.



$$\frac{B(T)}{C(T)} = \begin{cases} T \cdot \left[ 1 - e^{-\frac{1}{250}} \right] \approx \lambda T, & T \leq 906 \\ T \cdot \left[ e^{-\frac{1}{250} \cdot \frac{(T-906)}{T}} - e^{-\frac{1}{250}} \right], & T > 906 \end{cases} \quad (39)$$

$\frac{B(T)}{C(T)}$  is the reduction in the number of patients with metastasis in population  $w$  per individual exam.



$$\frac{\partial B}{\partial C} = \begin{cases} 0, & T \leq 906 \\ \frac{906}{91250} \cdot e^{[-(T-906)/250 \cdot T]}, & T > 906 \end{cases} \quad (40)$$

$\frac{\partial B}{\partial C}(T)$  is the marginal benefit per unit cost at a particular interexamination interval  $T$ . It represents the expected increase in the reduction of the number of patients with metastasis in population  $w$  per additional examination per year.

## VI Description of model M1

As mentioned in Section III, we hope to be able to modify the model one step at a time. Therefore, model M1 differs from model M0 only in the representation of the probability of no metastasis to date as a function of tumor size.

Probability of no metastasis to date,  $h(n)$ , is modeled as an arbitrary continuous monotonically non-increasing function of  $n$ . From the tumor growth law, we can derive the probability of no metastasis to date as a function of time,  $h(n(t))$ .

As with M0, we assume that  $t_{d,mamm} < t_{d,self}$ , since if it were not the case, all the tumors, whether already metastasized or not, would be detected by self-examination before being detected by a screening, and the screening would be irrelevant.

There are two distinct cases describing the relation between  $t_{d,mamm}$  and  $t_{d,self}$ . In the first case,  $t_{d,mamm} + T \leq t_{d,self}$ . In this case, all the tumors, whether already metastasized or not, get detected by a screening before being detected by a self-examination. Therefore, self-examination in this case is irrelevant. In the second case,  $t_{d,mamm} + T > t_{d,self}$ . Such relation allows a nonzero probability that a tumor is detected by self-examination before being detected by a screening. We will consider both cases in our analysis.

## VII Analysis of M1

- a) We first look at the behavior of a single tumor, assuming absence of any other tumors. In this model self-examination first comes into play. In the case when  $t_{d,mamm} + T \geq t_{d,self}$ , there exists a non-zero probability that a tumor is detected by self-examination before it is detected by mammography. In the case when  $t_{d,mamm} + T < t_{d,self}$ , the probability that a tumor is detected by self-examination before it is detected by mammography is zero, and we can ignore

self-examination. We want to derive  $P(T) = \Pr \left\{ \begin{array}{l} \text{a single tumor is detected} \\ \text{before it metastasizes} \\ \text{given screening interval } T \end{array} \right\}$ .

There are two separate cases to be considered.

- i)  $t_{d,mamm} + T < t_{d,self}$ . In this case we ignore self-examination, and the derivation is the same as in the case of M0. We conclude that

$$P(T) = \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt \quad (41)$$

- ii)  $t_{d,mamm} + T \geq t_{d,self}$ . In this case self-examination is relevant. Given that a tumor is detected, the probability that it is detected by mammography is  $\frac{t_{d,self}-t_{d,mamm}}{T}$ ,

and the probability that it gets detected by self-examination is  $1 - \frac{t_{d,self} - t_{d,mamm}}{T} = \frac{T + t_{d,mamm} - t_{d,self}}{T}$ .

$$Pr \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized} \\ \text{before detection} \end{array} \middle| \begin{array}{l} \text{tumor detected} \\ \text{by mammography} \end{array} \right\} = \frac{1}{t_{d,self} - t_{d,mamm}} \sum_{k=t_{d,mamm}}^{t_{d,self}} h(n(t))$$

$$\approx \frac{1}{t_{d,self} - t_{d,mamm}} \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt \quad (42)$$

$$Pr \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized} \\ \text{before detection} \end{array} \middle| \begin{array}{l} \text{tumor detected by} \\ \text{self-examination} \end{array} \right\} = h(n(t_{d,self})) \quad (43)$$

Therefore,

$$P(T) = \frac{t_{d,self} - t_{d,mamm}}{T} \cdot \frac{1}{t_{d,self} - t_{d,mamm}} \cdot \left[ \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt \right] +$$

$$+ \frac{t_{d,mamm} + T - t_{d,self}}{T} \cdot h(n(t_{d,self})) =$$

$$= \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} + \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T} \quad (44)$$

In summary,

$$P(T) = \begin{cases} \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt, & t_{d,mamm} + T \leq t_{d,self} \\ \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} + \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T}, & t_{d,mamm} + T > t_{d,self} \end{cases} \quad (45)$$

- b) As described in Section V, we measure benefit as the difference between the expected number of patients with one or more metastasized tumors per year in the absence of screenings, and the expected number of patients with one or more metastasized tumors per year in the presence of screenings. Similar to the analysis in Section IV for the model M0,

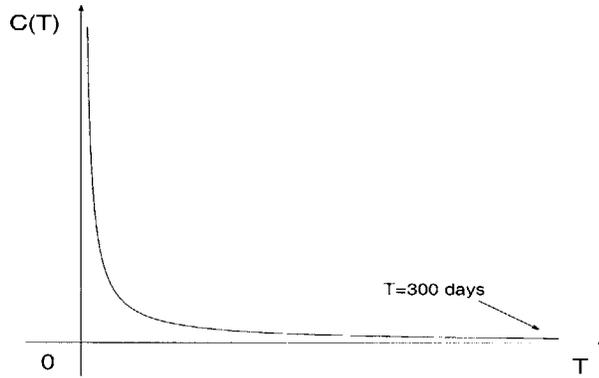
$$B(T) = w \cdot [e^{-\lambda(1-P(T))} - e^{-\lambda}] = w e^{-\lambda} \cdot [e^{\lambda P(T)} - 1] \approx w \lambda P(T) \quad (46)$$

Plugging in the value of  $P(T)$  into this expression, we get the following expression:

$$\begin{aligned}
 B(T) &= \begin{cases} w \cdot \left[ e^{-\lambda \cdot \left(1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right)} - e^{-\lambda} \right], & t_{d,mamm} + T \leq t_{d,self} \\ w \cdot \left[ e^{-\lambda \cdot \left(1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm}+T - t_{d,self}) \cdot h(n(t_{d,self}))}{T}\right)} - e^{-\lambda} \right], & t_{d,mamm} + T > t_{d,self} \end{cases} \\
 &\approx \begin{cases} \frac{w \lambda}{T} \cdot \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt, & t_{d,mamm} + T \leq t_{d,self} \\ \frac{w \lambda}{T} \cdot \left[ \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt + (T + t_{d,mamm} - t_{d,self}) \cdot h(n(t_{d,self})) \right], & t_{d,mamm} + T > t_{d,self} \end{cases} \quad (47)
 \end{aligned}$$

c) As described in Section V,

$$C(T) = \frac{w}{T} \quad (48)$$



d) We now proceed to derive the expression for the ratio of benefit to cost,  $\frac{B(T)}{C(T)} \approx \lambda T P(T)$ .

$$\frac{B(T)}{C(T)} = \begin{cases} \frac{w \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt \right)} - e^{-\lambda} \right]}{\frac{w}{T}}, & t_{d,mamm} + T \leq t_{d,self} \\ \frac{w \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm}+T-t_{d,self}) \cdot h(n(t_{d,self}))}{T} \right)} - e^{-\lambda} \right]}{\frac{w}{T}}, & t_{d,mamm} + T > t_{d,self} \end{cases}$$

$$= \begin{cases} T \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt \right)} - e^{-\lambda} \right], & t_{d,mamm} + T \leq t_{d,self} \\ T \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm}+T-t_{d,self}) \cdot h(n(t_{d,self}))}{T} \right)} - e^{-\lambda} \right], & t_{d,mamm} + T > t_{d,self} \end{cases}$$

(49)

e) We now derive the expression for the marginal benefit per unit cost,  $\frac{\partial B}{\partial C}$ .

$$\begin{aligned}
\frac{\partial B}{\partial C} &= \frac{-\frac{\partial B}{\partial T}}{-\frac{\partial C}{\partial T}} \\
&= \begin{cases} \frac{-\left(\frac{\lambda w}{T} h(n(t_{d,mamm}+T)) - \frac{\lambda w}{T^2} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right) \cdot \left[e^{-\lambda \left(1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right)}\right]}{\frac{w}{T^2}}, & t_{d,mamm} + T \leq t_{d,self} \\ \\ -\left(\frac{\lambda w \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T^2} + \frac{\lambda w h(n(t_{d,self}))}{T} - \frac{\lambda w (t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T^2}\right) \\ \cdot \left[e^{-\lambda \left(1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T}\right)}\right], & t_{d,mamm} + T > t_{d,self} \end{cases} \\
&= \begin{cases} \left(-\lambda T h(n(t_{d,mamm} + T)) + \lambda \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right) \cdot \left[e^{-\lambda \left(1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right)}\right], & t_{d,mamm} + T \leq t_{d,self} \\ \\ \left(\lambda (t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self})) + \lambda \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt - \lambda T h(n(t_{d,self}))\right) \cdot \left[e^{-\lambda \left(1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T}\right)}\right], & t_{d,mamm} + T > t_{d,self} \end{cases}
\end{aligned}$$

$$= \left\{ \begin{array}{l} \left( -\lambda T h(n(t_{d,mamm} + T)) + \lambda \int_{t_{d,mamm}}^{t_{d,mamm} + T} h(n(t)) dt \right) \cdot \\ \left[ e^{-\lambda \cdot \left( 1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm} + T} h(n(t)) dt \right)} \right], \quad t_{d,mamm} + T \leq t_{d,self} \\ \\ \left( \lambda (t_{d,mamm} - t_{d,self}) \cdot h(n(t_{d,self})) + \lambda \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt \right) \cdot \\ \left[ e^{-\lambda \cdot \left( 1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T} \right)} \right], \quad t_{d,mamm} + T > t_{d,self} \end{array} \right.$$

Now we use the above derivations to produce graphs based on the data provided by Jim Michaelson [1, 2, 4, 6]. Similar to M0, in this model we let  $n_{d,mamm}$  be the number of cells in a 7 mm diameter tumor, which is the size corresponding to the probability of detection by mammography of 50% [6, p.6]. We let  $n_{d,self}$  be the number of cells in a 20 mm diameter tumor, which is the size corresponding to the probability of detection by self-examination of 50% [1]. We assume that cell density is equal to  $10^8 \text{ cells/cm}^3$ . We take the doubling time of tumors to be 130 days [5], and use the exponential growth law. We take  $\lambda = \frac{1}{250} \text{ years}^{-1} = \frac{1}{91250} \text{ days}^{-1}$ . We assume that  $w = 1000$ . Based on these assumptions and on the fact that we take  $n_m$  be the number of cells in a tumor that is 1 mm in diameter, we have:

$$n(t) = n_m e^{rt} \quad (54)$$

$$r = 0.00533 \text{ days}^{-1} \quad (55)$$

$$n_m = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (0.05 \text{ cm})^3 = 52,333 \text{ cells} \quad (56)$$

$$n_{d,mamm} = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (0.35 \text{ cm})^3 = 17,950,333 \text{ cells} \quad (57)$$

$$n_{d,self} = 10^8 \frac{\text{cells}}{\text{cm}^3} \cdot \frac{4}{3} \cdot \pi \cdot (1 \text{ cm})^3 = 418,666,670 \text{ cells} \quad (58)$$

$$17,950,333 = 52,333 e^{0.00533 \cdot t_{d,mamm}}$$

$$t_{d,mamm} = 1095 \text{ days} \quad (59)$$

$$418,666,670 = 52,333 e^{0.00533 \cdot t_{d,self}}$$

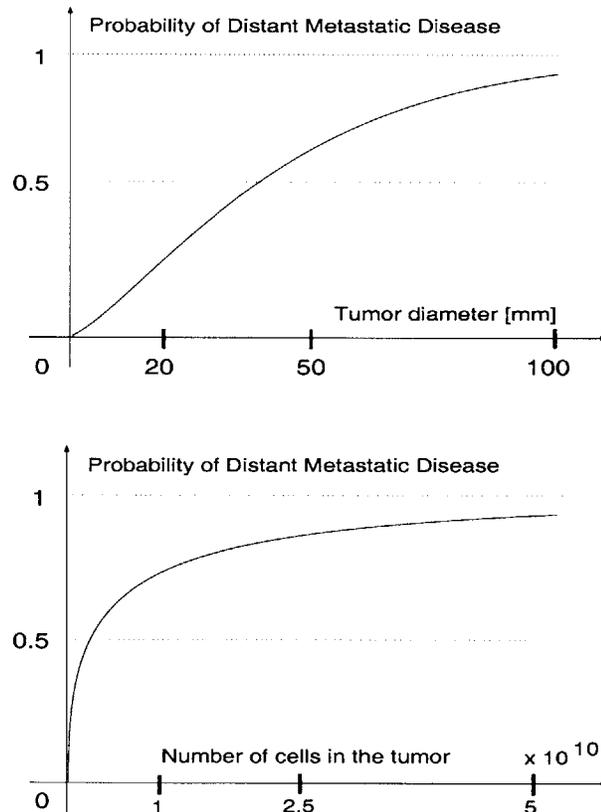
$$t_{d,self} = 1686 \text{ days} \quad (60)$$

We use the data and the curve fit provided by Jim Michaelson for the probability of distant

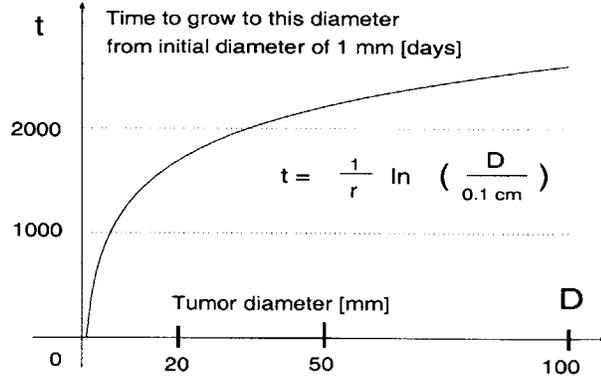
metastatic disease [4, p.4, p.15] to derive  $h(n(t))$ . The curve fit suggests

$$F(D) = \frac{1}{e^{0.0061 \cdot D^{1.3276}}}, \quad (61)$$

where  $F$  is the fraction of patients surviving breast cancer and  $D$  is the tumor diameter in millimeters. The graphs below demonstrate the relation between the fraction of patients surviving breast cancer and the tumor diameter in millimeters, between the fraction of patients surviving breast cancer and the number of cells in the tumor at the time of detection. We take these fractions  $F$  to be the probability of tumor metastasis corresponding to each tumor size measured in terms of the tumor diameter assuming spherical geometry, or in terms on the number of cells.



We use the exponential growth law to derive  $h(n(t))$ : the probability of no metastasis to date as a function of tumor age. The graph below demonstrates the relation between tumor age and the tumor diameter assuming exponential growth law and spherical geometry.

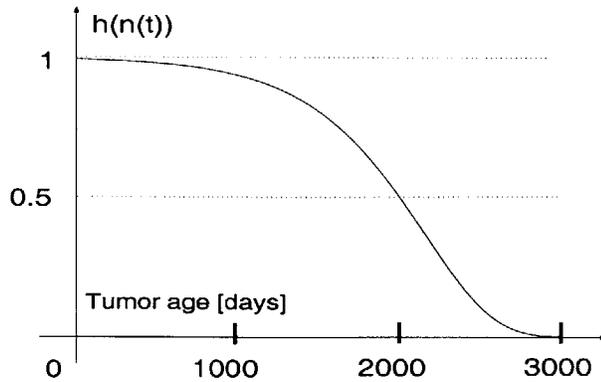


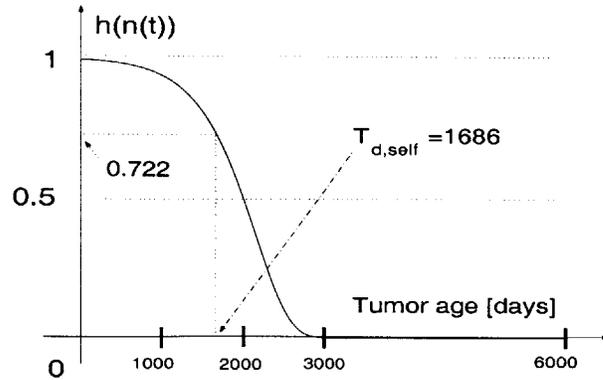
$$F = \frac{1}{e^{0.0061 \cdot D^{1.3276}}} \quad (62)$$

$$F = \frac{1}{e^{0.0061 \cdot \left(20 \cdot \sqrt[3]{\frac{N}{10^8 \cdot \frac{4}{3} \cdot \pi}}\right)^{1.3276}}}, \text{ where } N \text{ is the number of cells in the tumor} \quad (63)$$

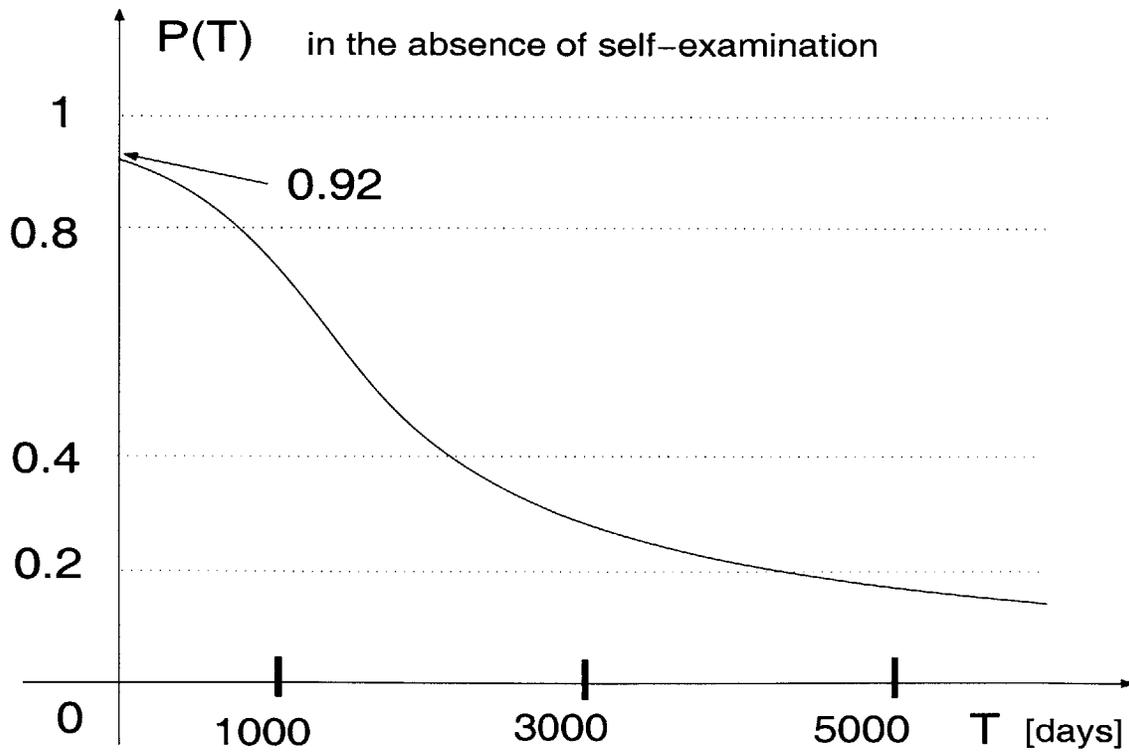
$$t = \frac{1}{0.00533} \cdot \ln\left(\frac{N}{10^8 \cdot \frac{4}{3} \cdot \pi \cdot (0.05)^3}\right), \text{ where } t \text{ is the age of the tumor} \quad (64)$$

$$\begin{aligned} h(n(t)) &= \frac{1}{e^{0.0061 \cdot \left(20 \cdot \sqrt[3]{\frac{10^8 \cdot \frac{4}{3} \cdot \pi \cdot (0.05)^3 \cdot e^{[0.00533 t]}}{10^8 \cdot \frac{4}{3} \cdot \pi}}\right)^{1.3276}}} \\ &= \frac{1}{e^{0.0061 \cdot \left(20 \cdot \sqrt[3]{(0.05)^3 \cdot e^{0.00533 t}}\right)^{1.3276}}} \\ &= \frac{1}{e^{0.0061 \cdot \left(\sqrt[3]{e^{0.00533 t}}\right)^{1.3276}}} \end{aligned} \quad (65)$$

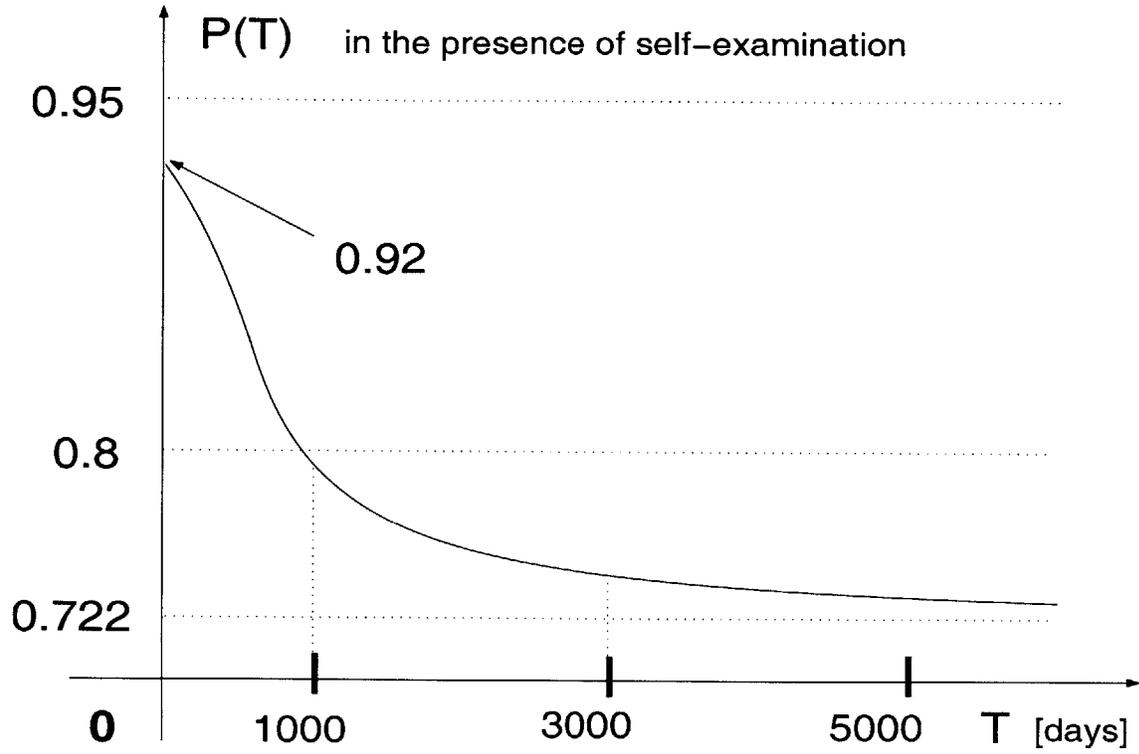




We now turn to the plots of  $P(T)$ ,  $B(T)$ ,  $\frac{B(T)}{C(T)}$  and  $\frac{\partial B}{\partial C}$ . Below is the plot of  $P(T)$  in the absence of self-examination, corresponding to equation (41).

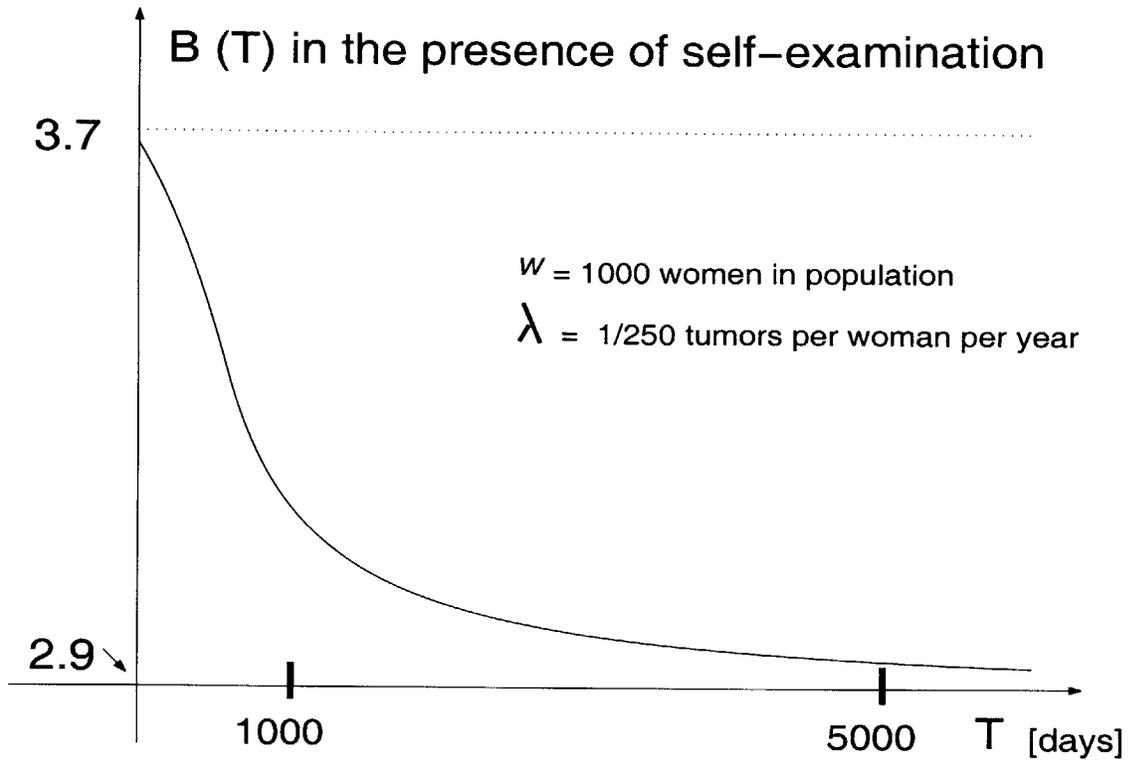


Following are the plots in the presence of self-examination.



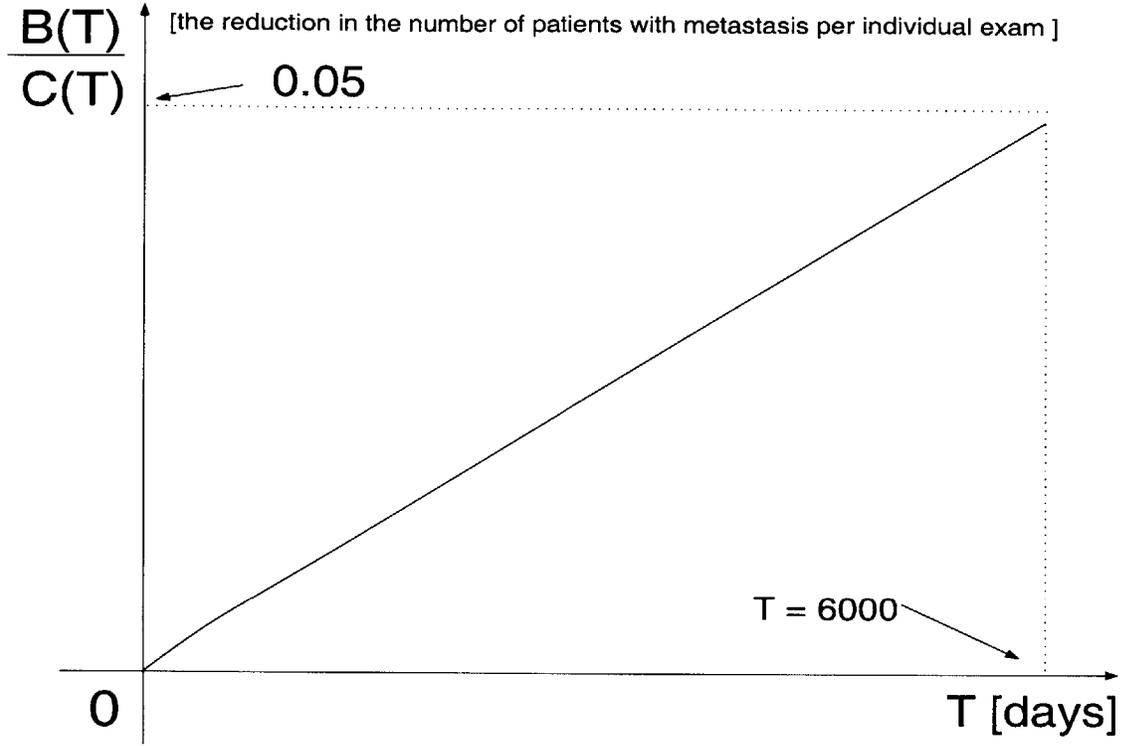
$$P(T) = \begin{cases} \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt, & T \leq t_{d,self} - t_{d,mamm} = 591 \text{ days} \\ \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} + \frac{(t_{d,mamm}+T-t_{d,self}) \cdot h(n(t_{d,self}))}{T}, & T > t_{d,self} - t_{d,mamm} = 591 \text{ days} \end{cases} \quad (66)$$

$P(T)$  is the probability that a single tumor is detected before metastasis. In the presence of self-examination,  $\lim_{T \rightarrow \infty} P(T) \rightarrow h(t_{d,self}) \approx 0.722$ .



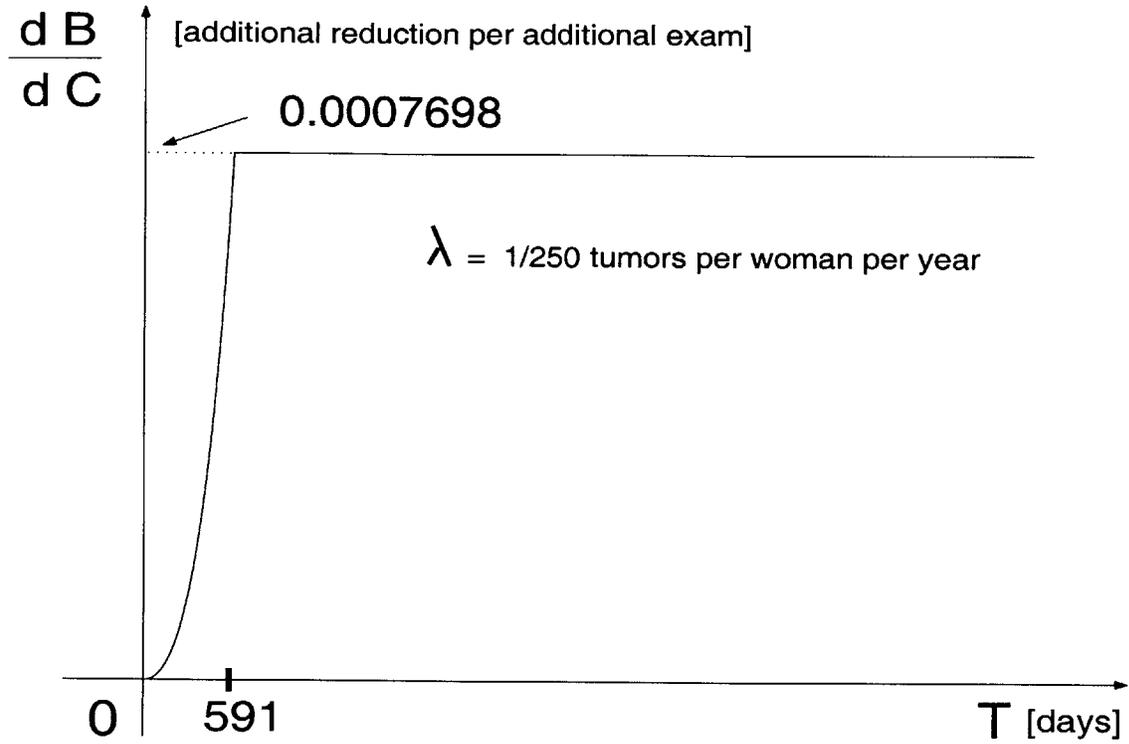
$$B(T) = \begin{cases} w \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt \right)} - e^{-\lambda} \right], & T \leq t_{d,self} - t_{d,mamm} = 591 \text{ days} \\ w \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm}+T - t_{d,self}) \cdot h(n(t_{d,self}))}{T} \right)} - e^{-\lambda} \right], & T > t_{d,self} - t_{d,mamm} = 591 \text{ days} \end{cases} \quad (67)$$

B(T) is the reduction in the number of patients with metastasis in population  $w$  per year.



$$\frac{B(T)}{C(T)} = \begin{cases} T \cdot \left[ e^{-\lambda \cdot \left(1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt\right)} - e^{-\lambda} \right] \approx \lambda \int_{t_{d,mamm}}^{t_{d,mamm}+T} h(n(t)) dt, & T \leq t_{d,self} - t_{d,mamm} = 591 \text{ days} \\ T \cdot \left[ e^{-\lambda \cdot \left(1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm}+T-t_{d,self}) \cdot h(n(t_{d,self}))}{T}\right)} - e^{-\lambda} \right] \approx & \\ \approx \lambda \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt + \lambda(t_{d,mamm} - t_{d,self} + T) \cdot h(n(t_{d,self})), & T > t_{d,self} - t_{d,mamm} = 591 \text{ days} \end{cases} \quad (68)$$

$\frac{B(T)}{C(T)}$  is the reduction in the number of patients with metastasis in population  $w$  per individual exam. For values of  $T > 591$  days, the slope of the curve is roughly consistent with  $\lambda \cdot h(n(t_{d,self}))$ , as in the expression above.



$$\frac{\partial B}{\partial C} = \begin{cases} \left( -\lambda T h(n(t_{d,mamm} + T)) + \lambda \int_{t_{d,mamm}}^{t_{d,mamm} + T} h(n(t)) dt \right) \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{1}{T} \int_{t_{d,mamm}}^{t_{d,mamm} + T} h(n(t)) dt \right)} \right], & T \leq t_{d,self} - t_{d,mamm} = 591 \text{ days} \\ \left( \lambda (t_{d,mamm} - t_{d,self}) \cdot h(n(t_{d,self})) + \lambda \int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt \right) \cdot \left[ e^{-\lambda \cdot \left( 1 - \frac{\int_{t_{d,mamm}}^{t_{d,self}} h(n(t)) dt}{T} - \frac{(t_{d,mamm} + T - t_{d,self}) \cdot h(n(t_{d,self}))}{T} \right)} \right], & T > t_{d,self} - t_{d,mamm} = 591 \end{cases} \quad (69)$$

$\frac{\partial B}{\partial C}(T)$  is the marginal benefit per unit cost at a particular interexamination interval  $T$ . It represents the expected increase in the reduction of the number of patients with metastasis in population  $w$  per additional examination per year.

## VIII Description of model M2

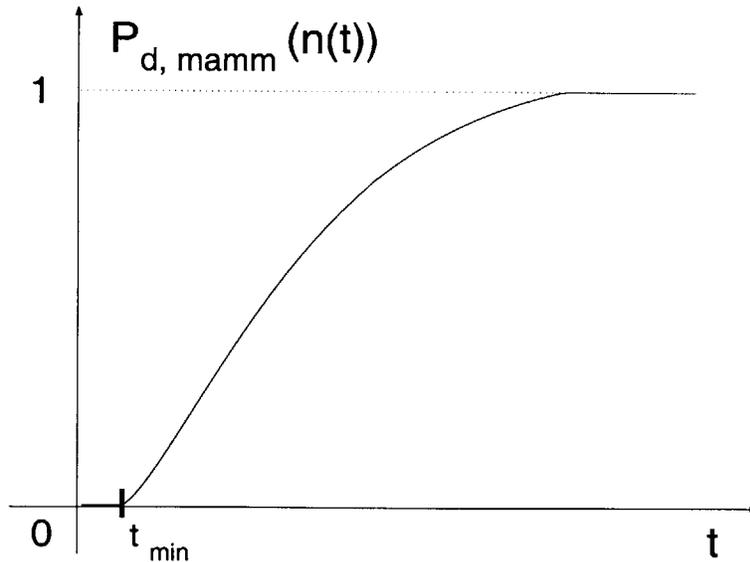
We continue to modify the model one step at a time. In model M2 we change the representation of the probability of detection by mammography.

Probability of detection by mammography is modeled as an arbitrary continuous monotonically non-decreasing function of  $n$ , denoted by  $P_{d,mamm}$ . We can use the tumor growth law to express the probability of detection by mammography as a function of tumor age.

Unlike M1, in M2 self-examination is relevant for all values of  $T$ , since for any value of  $T$  there is a non-zero probability that a tumor is not detected at any of the mammographic examination preceding the time when the tumor reaches  $n_{d,self}$  cells in size. Therefore, we do not split the analysis into two parts like we did for both M0 and M1.

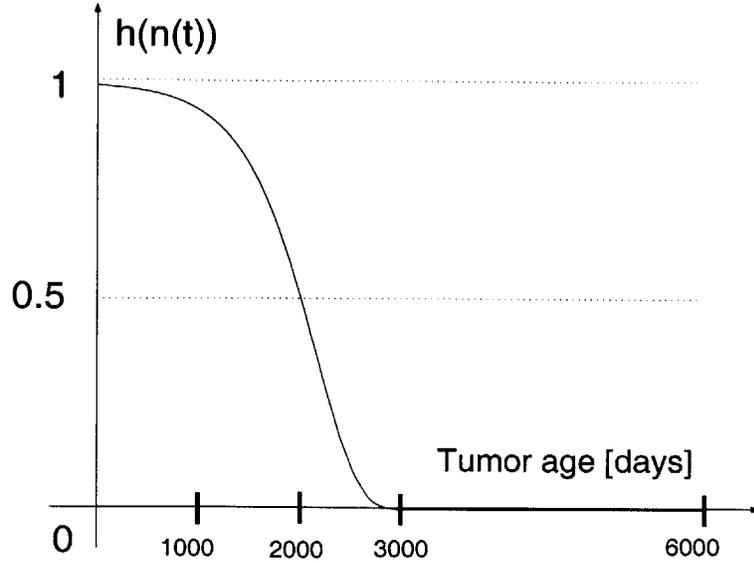
## IX Analysis of M2

Again, we look at the behavior of a single tumor in the absence of other tumors. In this model we do not have a threshold for detectability by mammographic examination, and we represent  $P_{d,mamm}(n(t))$ , the probability of detection by mammography on a single exam, as a continuous non-decreasing function of  $t$ . We assume that  $P_{d,mamm}(n(t)) = 0$  for  $t \leq t_{min}$ , where  $t_{min}$  is some value of tumor age. The graph below demonstrates this assumption, and Jim Michaelson's data supports this assumption.

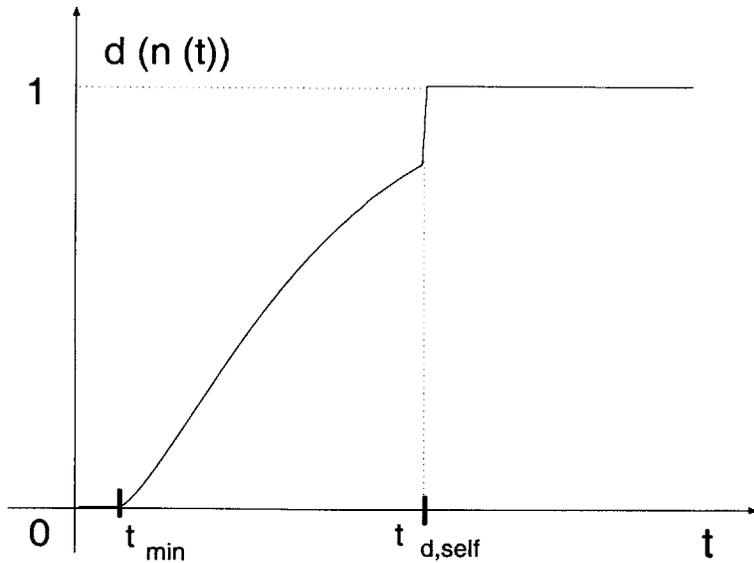


From Section VI we have that  $h(n(t))$  is a continuous non-increasing function of  $t$ , as shown below.

We need to find the probability of no metastasis before detection for a single tumor. Since in M2

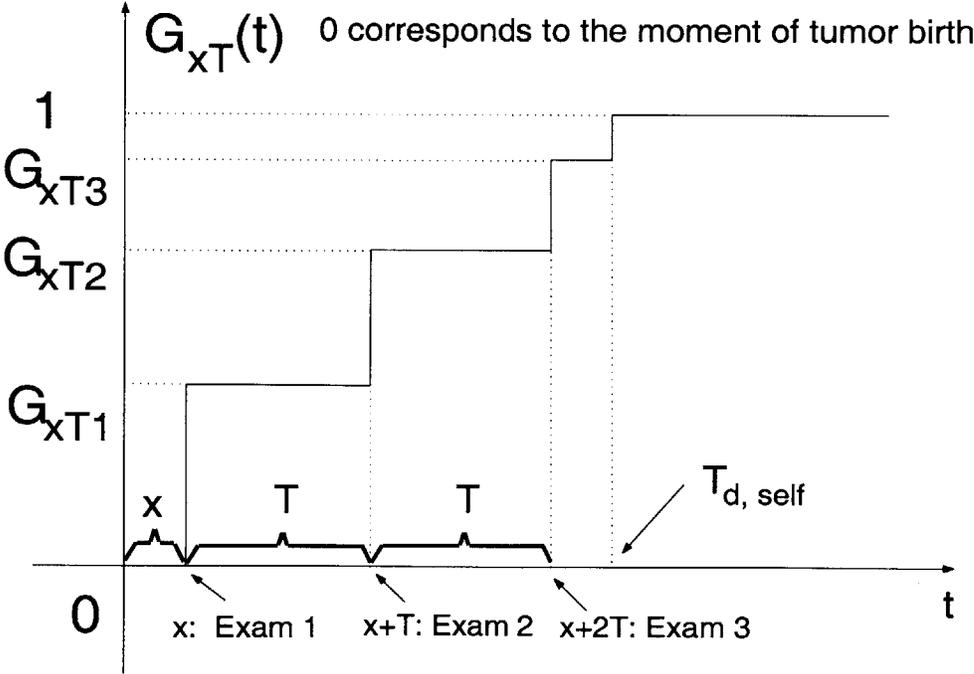


the probability of detection by self-examination is modeled as a step function (see Section VII), the tumor can be found either by mammography at ages between  $t_{min}$  and  $t_{d,self}$ , or by self-examination at the age of  $t_{d,self}$ . We denote *the probability of detection by mammography or by self-examination* by  $d(n(t))$ , and base our derivation of  $P(T)$  on  $d(n(t))$  and  $h(n(t))$ . The probability of detection by mammography or by self-examination,  $d(n(t))$ , is plotted below.

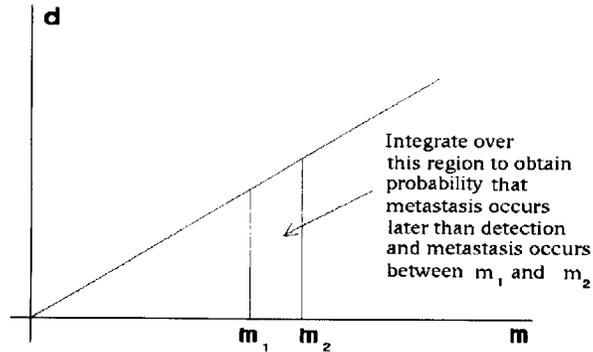


In order to derive  $P(T)$ , we look at the probability that one random variable, the time of detection, is less than another random variable, the time of metastasis. Such probability represents the event that detection occurs before metastasis, which is what we are interested in. In this case we need to deal with two cumulative distribution functions. One of these is  $F(t) = 1 - h(n(t))$ . Another is  $G(t) = Pr \{detection\ at\ some\ \tau \leq t\}$ . The derivation of  $G(t)$  is based on  $d(n(t))$

and takes into account the fact that, unlike metastasis, detection can only happen at discrete time intervals for  $t < t_{d,self}$ . For each tumor, the probability of detection at some  $\tau \leq t$  depends on the interscreening interval  $T$  and on the age of the tumor at the first exam in its lifetime, denoted by  $x$ . We denote the probability of detection at some  $\tau \leq t$  given the interscreening interval  $T$  and the age at the first exam  $x$  by  $G_{xT}(t)$ . Below is the generic plot of  $G_{xT}(t)$ . In this plot below,  $G_{xT1}$  corresponds to the probability that the tumor is detected on the first exam in the life of the tumor, given the interscreening interval  $T$ , and the age at the first exam  $x$ . Similarly,  $G_{xT2}$  corresponds to the probability that the tumor is detected by the second exam in the life of the tumor, given the interscreening interval  $T$ , and the age at the first exam  $x$ , and so on. We denote the probability that detection occurs before metastasis given the tumor age at the first exam  $x$  by  $P_x(T)$ , and the probability that the tumor is detected on the first exam given that its age at the first exam is  $x$  by  $G_{x1}$ . Similarly, we denote the probability that the tumor is detected by the second exam given that its age at the first exam is  $x$  by  $G_{x2}$ , and the probability that the tumor is detected by the  $k^{th}$  exam given that its age at the first exam is  $x$  by  $G_{xk}$ .



We can derive the probability of no metastasis before detection for a given age at the first exam  $x$  as follows. We know that  $F'(t)$  is the metastasis density, and  $G'_{x,T}(t)$  is the detection by mammography or self-examination density given the interexamination interval  $T$  and age at the first exam  $x$ . We can find the probability that detection happens earlier than metastasis by integrating the joint density of  $F'(t)$  and  $G'_{x,T}(t)$  over the region where  $d$  (corresponding to detection) is smaller than  $m$  (corresponding to metastasis), for each value of the age at the first mamographic examination  $x$ . The joint density for  $d$  and  $m$  factors into a product of  $F(t)$  and  $G_{xT}(t)$ , because we assume conditional independence of metastasis and detection give the tumor size  $n$ . We break up the region of integration into several smaller regions, intergrate over each of them, as illustrated in the graph below, and add the results to obtain  $P_x(T)$ , the probability that metastasis occurs later than detection for a given age at the first exam  $x$ , as a function of  $T$ .



In our derivation, we break up the region of integration into smaller regions corresponding to time intervals between two consecutive mammographic examinations. It follows that

$$\begin{aligned}
P_x(T) &= Pr \left\{ \begin{array}{l} \text{metastasis occurs} \\ \text{later than} \\ \text{detection} \end{array} \middle| \begin{array}{l} \text{tumor is } x \text{ days} \\ \text{old at its first} \\ \text{examination} \end{array} \right\} \\
&= \int_0^\infty \int_{d=0}^m F'(m) G'_{x,T}(d) dd dm \\
&= \int_0^\infty F'(t) G_{x,T}(t) dt \\
&= G_{x1} \cdot [F(t_2) - F(t_1)] + G_{x2} \cdot [F(t_3) - F(t_2)] + \dots + \\
&+ G_{xk} \cdot [F(t_{d,self}) - F(t_k)] + 1 - F(t_{d,self})
\end{aligned}$$

where  $t_1, t_2, \dots t_k$  are the times of first, second, etc. mammographic exams

in the lifetime of the tumor

(70)

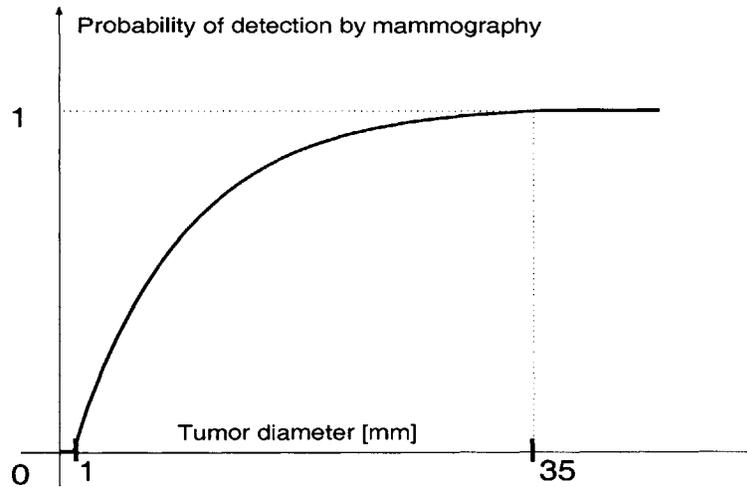
Now we turn to the data provided by Jim Michaelson to derive the values of  $G_{xT1}$ ,  $G_{xT2}$ , etc. for different values of  $T$  and  $x$  [1, 2, 4, 6]. First, we turn to his data for the probability of detection by mammography as a function of tumor size and do a curve fit for this data to derive a realistic continuous function for  $P_{d,mamm}(n(t))$ . Based on the data [2], we produce the following curve fit:

$$H(D) = \begin{cases} 1 - e^{-\frac{1-D}{8}}, & D \geq 1 \text{ mm} \\ 0, & D < 1 \text{ mm} \end{cases} \quad \text{where } D \text{ is the diameter of the tumor in millimeters} \quad (71)$$

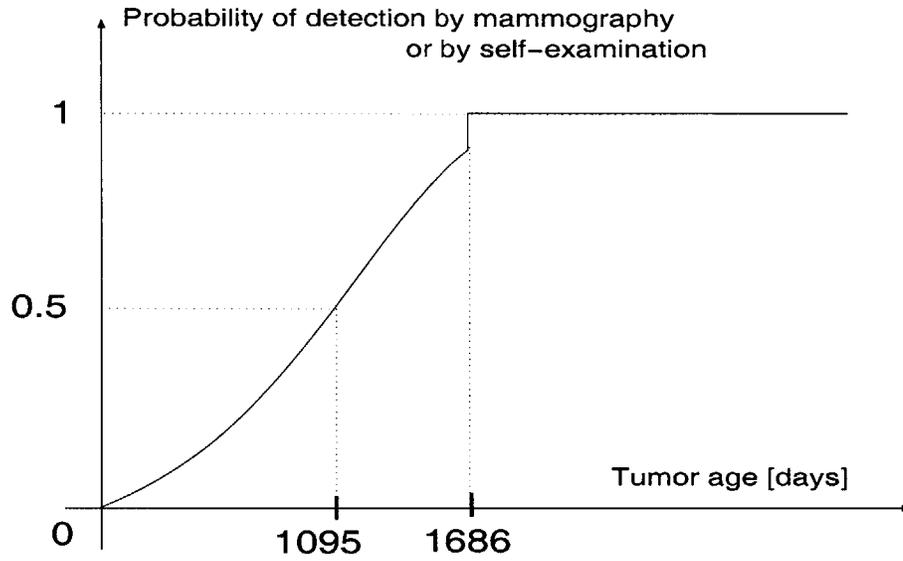
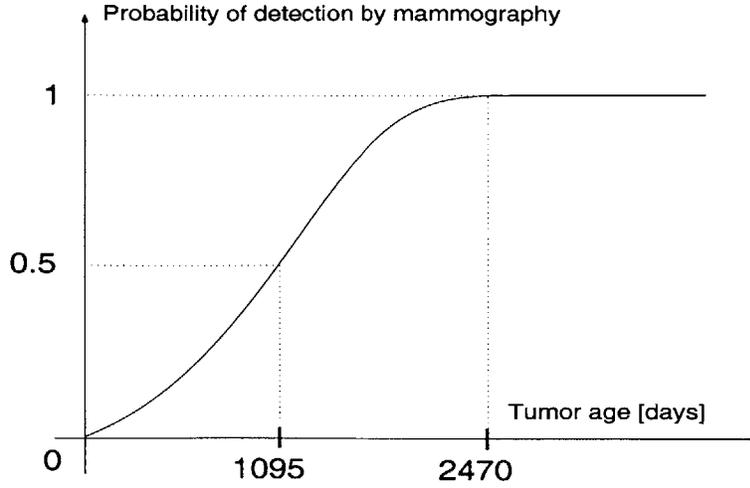
$$H(N) = 1 - e^{-\frac{1-20 \cdot \sqrt[3]{\frac{10^8 \cdot N}{3 \cdot \pi}}}{8}}, \quad \text{where } N \text{ is the number of cells in the tumor} \quad (72)$$

$$\begin{aligned} H(t) &= 1 - e^{-\frac{1-20 \cdot \sqrt[3]{(0.05)^3 e^{0.00533t}}}{8}}, \quad \text{where } t \text{ is the age of the tumor in days} \\ &= 1 - e^{-\frac{1 - \sqrt[3]{e^{0.00533t}}}{8}} \end{aligned} \quad (73)$$

Below are the graphs corresponding to equations (78) and (80), respectively.



Accounting for self-examination, we modify the data plotted above for values of tumor age greater than 1686 days to arrive at  $d(n(t))$ , the probability of detection by mammography or by self-examination as a function of tumor age, plotted below.



Using the data plotted in this last graph, we derive the values for  $G_{xT1}$ ,  $G_{xT2}$ , etc. for all relevant values of  $x$  and  $T$ . For each  $T$  and  $x$ , we proceed as follows:

$$G_{xT1} = Pr \{ \text{detection occurs at first exam} \} \quad (74)$$

$$G_{xT2} - G_{xT1} = Pr \left\{ \begin{array}{l} \text{detection occurs on second exam} \\ \text{and does not occur at first exam} \end{array} \right\}$$

$$= (1 - H(t_1)) \cdot H(t_2) = (1 - G_{xT1}) \cdot H(t_{xT2}) \quad (75)$$

$$G_{xT2} = G_{xT1} + (1 - G_{xT1}) \cdot H(t_{xT2}) \quad (76)$$

$$G_{xT3} = G_{xT2} + (1 - G_{xT2}) \cdot H(t_3) \quad (77)$$

⋮

$$G_{xTn} = G_{xT(n-1)} + (1 - G_{xT(n-1)}) \cdot H(t_n) \quad (78)$$

Using the values for  $G_{xT_1}$ ,  $G_{xT_2}$ , etc. for each  $x$  and  $T$  derived as above, it does not appear feasible to bring the expression for  $P_x(T)$  in equation (70) to a closed form, so we have to rely on a numerical algorithm to compute the value of  $P_x(T)$  for different values of  $T$ . Further, we compute the value of  $P(T)$  from the set of values for  $P_x(T)$  corresponding to different values of  $x$  using the fact that tumor age at the first exam is uniformly distributed in time given the interexamination interval  $T$ . We use Matlab to implement this numerical algorithm (see Appendix I.1 for the Matlab code). In this algorithm, we simultaneously loop through all possible values of  $T$  and all possible values of  $x$ , and find the corresponding values of  $G_{xT_1}$ ,  $G_{xT_2}$ , ...,  $G_{xT_k}$  for all relevant values of  $T$  and possible values of  $x$  given the value of  $T$ . Then for each  $T$  we average the values of  $G_{xT_1}$  for all values of  $x \leq T$  to obtain the probability that the tumor is detected at the first examination for a given value of  $T$ . Similarly, for each  $T$  we average the values of  $G_{xT_2}$  to obtain the probability that the tumor is detected by the second examination for a given value of  $T$ , etc. This way we obtain  $P(T) = \frac{1}{T} \cdot \int_0^T P_x(T) dx$ . We test the correctness on this algorithm by running it on the data with the assumptions of model M1. The algorithm produces results that coincide with the results for M1 obtained analytically, giving some confidence that the algorithm is correct and reliable.

To find the values of  $B(T)$ ,  $\frac{B(T)}{C(T)}$ , and  $\frac{\partial B}{\partial C}$  we rely on the expressions of these functions as a function of  $P(T)$ , as below.

$$B(T) = w \cdot \left[ e^{-\lambda \cdot (1-P(T))} - e^{-\lambda} \right] = w e^{-\lambda} \cdot \left[ e^{\lambda P(T)} - 1 \right] \approx w \lambda P(T) \quad (79)$$

$$C(T) = \frac{w}{T} \quad (80)$$

$$\frac{B(T)}{C(T)} = T e^{-\lambda} \cdot \left[ e^{\lambda P(T)} - 1 \right] \approx T \lambda P(T) \quad (81)$$

$$\frac{\partial B}{\partial C} = \frac{-\frac{\partial B}{\partial T}}{-\frac{\partial C}{\partial T}} = \frac{-w \cdot e^{-\lambda} \cdot \lambda \cdot e^{\lambda P(T)} \cdot P'(T)}{\frac{w}{T^2}} \approx \frac{-w \cdot \lambda \cdot P'(T)}{\frac{w}{T^2}} = -T^2 \lambda P'(T) \quad (82)$$

These functions are plotted on the subsequent pages.

Alternatively, we can approach the problem of deriving  $P(T)$  for all values of  $T$  by looking at each mammographic examination individually using  $h(n(t))$  and  $d(n(t))$ . We can first derive the probability that a single tumor is detected at the first mammographic examination in its life and that it has not metastasized before this detection. Next we can derive the probability that a single mammographic tumor is detected at the second mammographic examination in its life and that it has not metastasized before this detection, given that it has not been detected at the first examination.

We can proceed this way to account for all the examinations in the life of the tumor, and for the probability of detection by self-examination, and sum all these probabilities to arrive at  $P(T)$ . Since  $d(n(t)) = 1$  for  $t \geq T_{abs}$ , we will have a finite number of terms in the summation.

$$\begin{aligned}
P(T) &= \sum_m \Pr \left\{ \begin{array}{l} \text{tumor is first detected} \\ \text{at } m^{\text{th}} \text{ examination} \end{array} \cap \begin{array}{l} \text{tumor has not metastasized} \\ \text{by } m^{\text{th}} \text{ examination} \end{array} \right\} + \\
&+ \Pr \left\{ \begin{array}{l} \text{tumor is detected} \\ \text{by self-examination} \end{array} \cap \begin{array}{l} \text{tumor has not metastasized} \\ \text{by the time of detection} \end{array} \right\} = \\
&= \frac{1}{T} \cdot \sum_{k=1}^T \Pr \left\{ \begin{array}{l} \text{tumor is detected} \\ \text{at } k^{\text{th}} \text{ day} \end{array} \right\} \cdot \left\{ \begin{array}{l} \text{tumor has not metastasized} \\ \text{by } k^{\text{th}} \text{ day} \end{array} \right\} + \\
&+ \frac{1}{T} \cdot \sum_{k=T+1}^{2T} \left[ \Pr \left\{ \begin{array}{l} \text{tumor is} \\ \text{detected} \\ \text{at } k^{\text{th}} \text{ day} \end{array} \right\} \cdot \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized by} \\ k^{\text{th}} \text{ day} \end{array} \right\} \cdot \Pr \left\{ \begin{array}{l} \text{tumor not} \\ \text{detected at } 1^{\text{st}} \\ \text{examination} \end{array} \right\} \right] + \\
&+ \frac{1}{T} \cdot \sum_{k=2T+1}^{3T} \left[ \Pr \left\{ \begin{array}{l} \text{tumor is} \\ \text{detected} \\ \text{at } k^{\text{th}} \text{ day} \end{array} \right\} \cdot \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized by} \\ k^{\text{th}} \text{ day} \end{array} \right\} \cdot \Pr \left\{ \begin{array}{l} \text{tumor not} \\ \text{detected at } 2^{\text{nd}} \\ \text{examination} \end{array} \right\} \right] + \\
&\vdots \\
&+ \frac{1}{T} \cdot \sum_{k=nT+1}^{nT+T} \left[ \Pr \left\{ \begin{array}{l} \text{tumor is} \\ \text{detected} \\ \text{at } k^{\text{th}} \text{ day} \end{array} \right\} \cdot \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized by} \\ k^{\text{th}} \text{ day} \end{array} \right\} \cdot \Pr \left\{ \begin{array}{l} \text{tumor not} \\ \text{detected at } n^{\text{th}} \\ \text{examination} \end{array} \right\} \right] + \\
&+ \Pr \left\{ \begin{array}{l} \text{tumor is detected by} \\ \text{self-examination} \end{array} \right\} \cdot \left\{ \begin{array}{l} \text{tumor has not} \\ \text{metastasized by} \\ \text{time of detection} \end{array} \right\} \cdot \Pr \left\{ \begin{array}{l} \text{tumor not detected} \\ \text{before detection by} \\ \text{self-examination} \end{array} \right\},
\end{aligned}$$

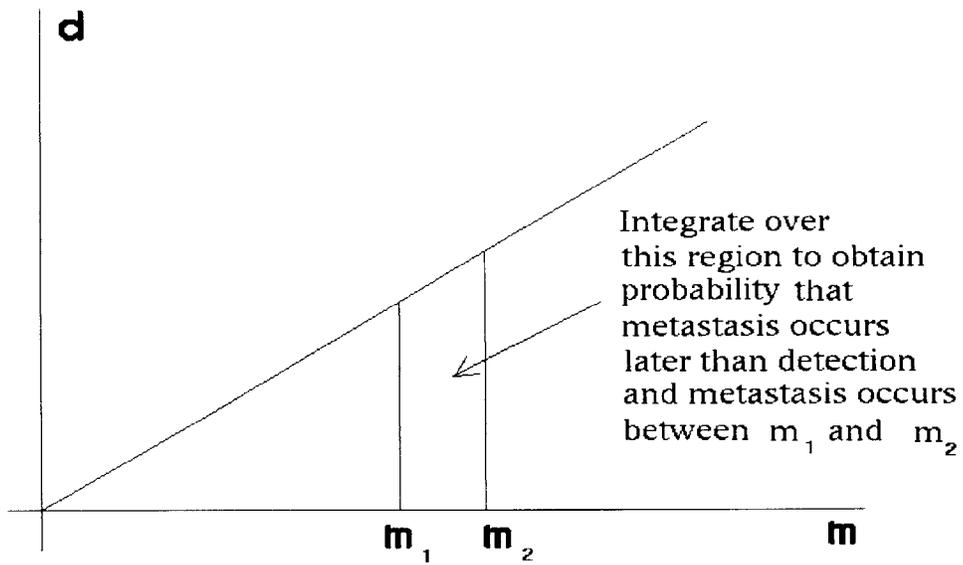
where  $n$  is the smallest integer such that  $nT + T \geq t_{d,self}$  (83)

$$\begin{aligned}
P(T) &= \frac{1}{T} \cdot \left[ \sum_{k=1}^T d(n(k)) \cdot h(n(k)) + \sum_{k=T+1}^{2T} d(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] \right] + \\
&+ \sum_{k=2T+1}^{3T} d(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] + \dots \\
&+ \sum_{k=nT+1}^{nT+T} nT + Td(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] \Big] + \\
&+ \Pr \left\{ \begin{array}{l} \text{tumor is detected} \\ \text{by self-examination} \end{array} \cap \begin{array}{l} \text{tumor has not metastasized} \\ \text{by the time of detection} \end{array} \right\} =
\end{aligned}$$

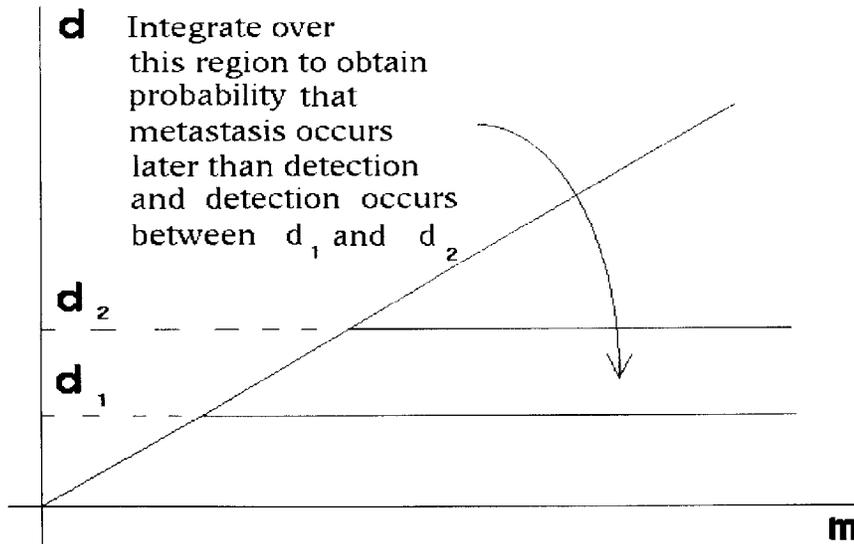
$$\begin{aligned}
&= \frac{1}{T} \cdot \left[ \sum_{k=1}^T d(n(k)) \cdot h(n(k)) + \sum_{k=T+1}^{2T} d(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] + \right. \\
&+ \sum_{k=2T+1}^{3T} d(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] + \dots \\
&+ \left. \sum_{k=nT+1} nT + Td(n(k)) \cdot h(n(k)) \cdot [1 - d(n(k-T))] \right] + \tag{84} \\
&+ \frac{1}{T} \cdot \sum_{k=1}^T [1 - d(n(t_{d, self} - k))] \cdot h(n(t_{d, self})) \tag{85}
\end{aligned}$$

These two approaches differ only in the way the region of intergration is broken up. In the first approach, we are summing the probabilities of disjoint events that metastasis occurs between two consecutive mammographic examinations ( $t_1$  and  $t_2$ ;  $t_2$  and  $t_3$ , etc), and that detection occurs before metastasis. In the second approach, we are summing the probabilities of disjoint events that detection occurs at a particular mammographic examination ( $t_1$ ,  $t_2$ , etc.) and that metastasis occurs at any time after this detection. The two approaches are compared in the graphs below.

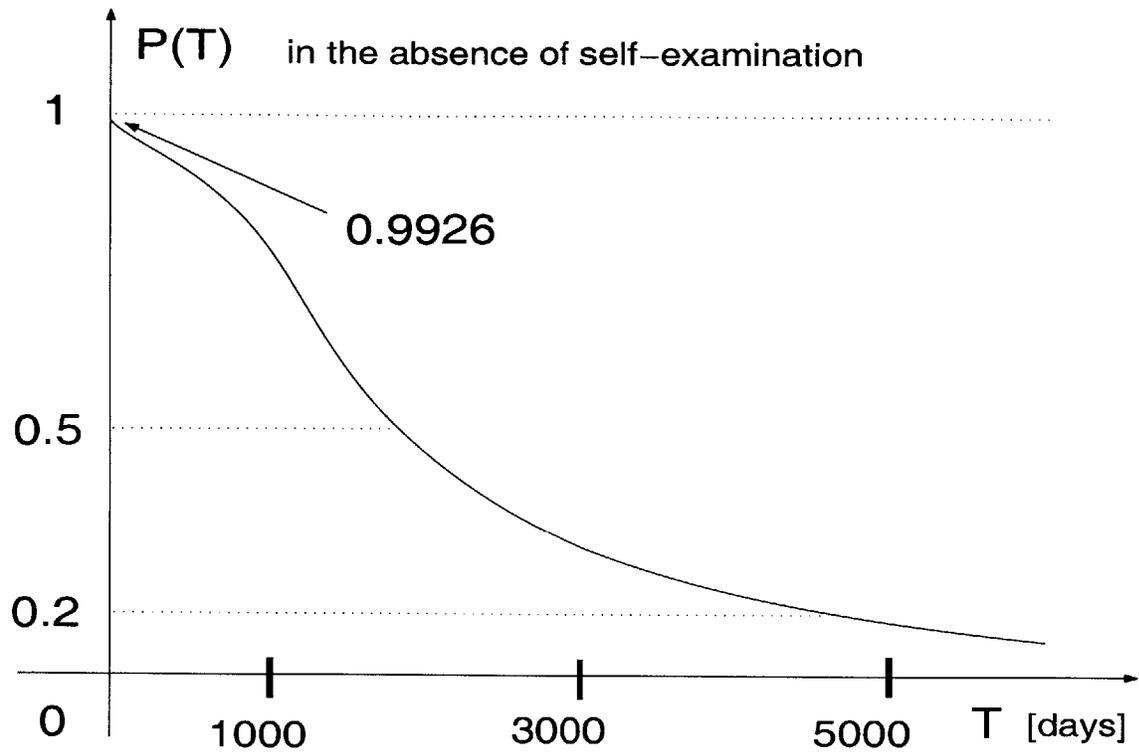
In both these approaches, we are assuming that the outcomes of all mammographic examinations are independent from each other. This assumption becomes unrealistic when mammographic examinations are close to each other, since if the probability that a present tumor of size  $n_1$  is not detected at a mammographic examination is  $\epsilon \geq 0$  and the probability of detection by mammography is a non-decreasing function of tumor size, then the probability that this tumor is detected after  $n$  mammographic examinations is upper bounded by  $1 - \epsilon^n$ , which approaches 1 for large  $n$ . Therefore, in this model  $P(T)$  comes out disproportionately large for smaller values of  $T$ , since smaller values of  $T$  correspond to more frequent mammographic examinations.



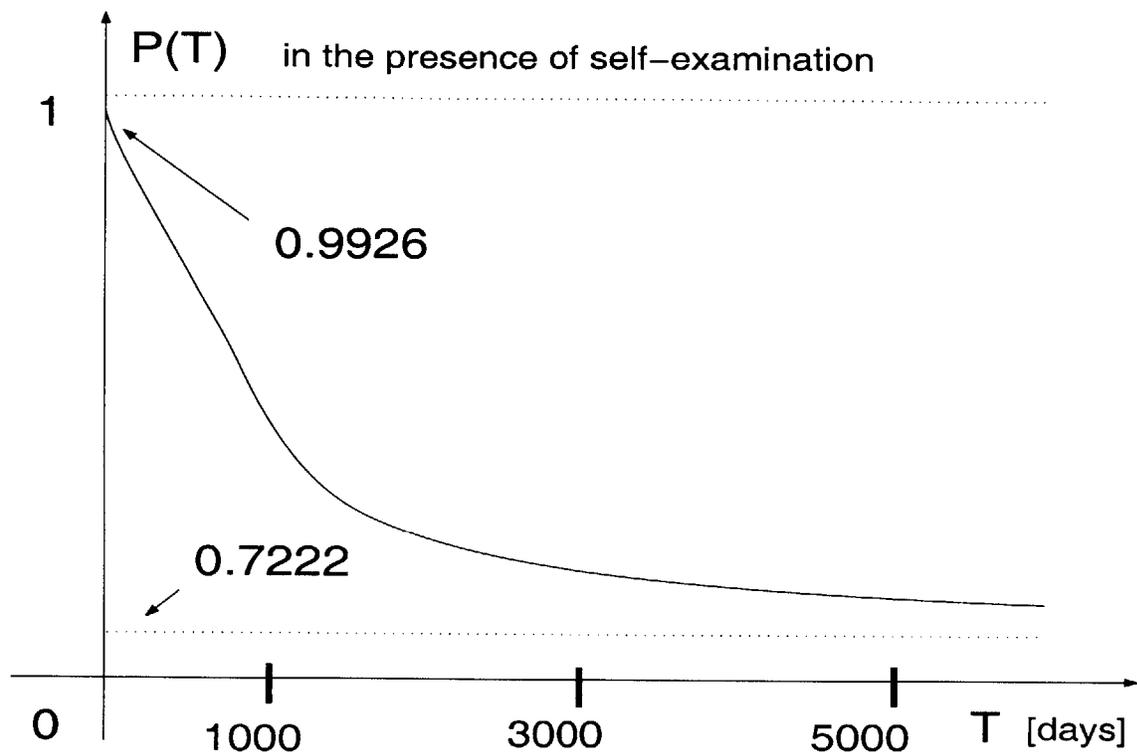
First Approach



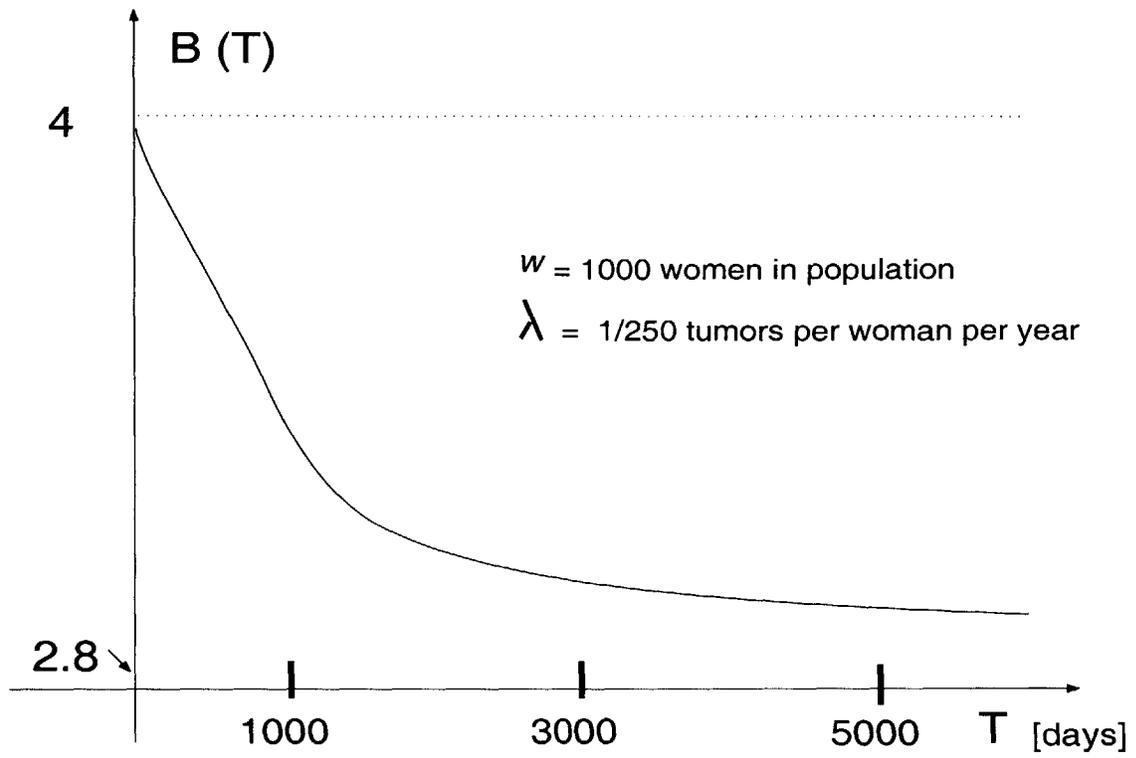
Second Approach



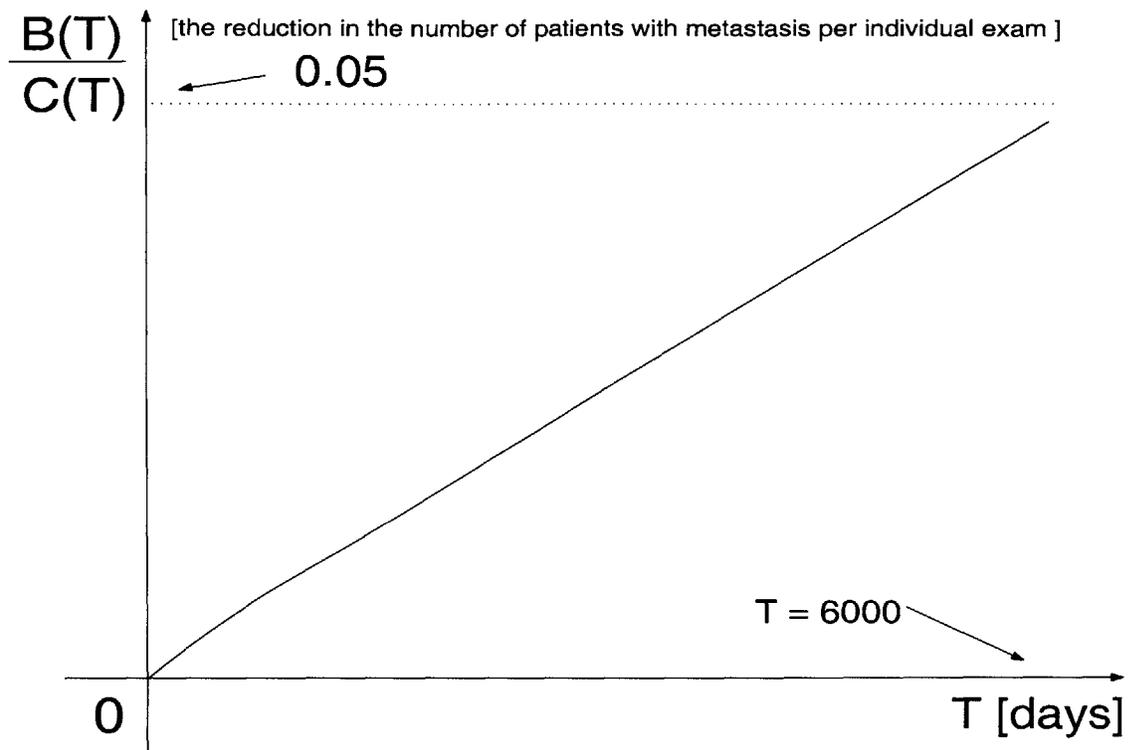
$P(T)$  is the probability that a single tumor is detected before metastasis.



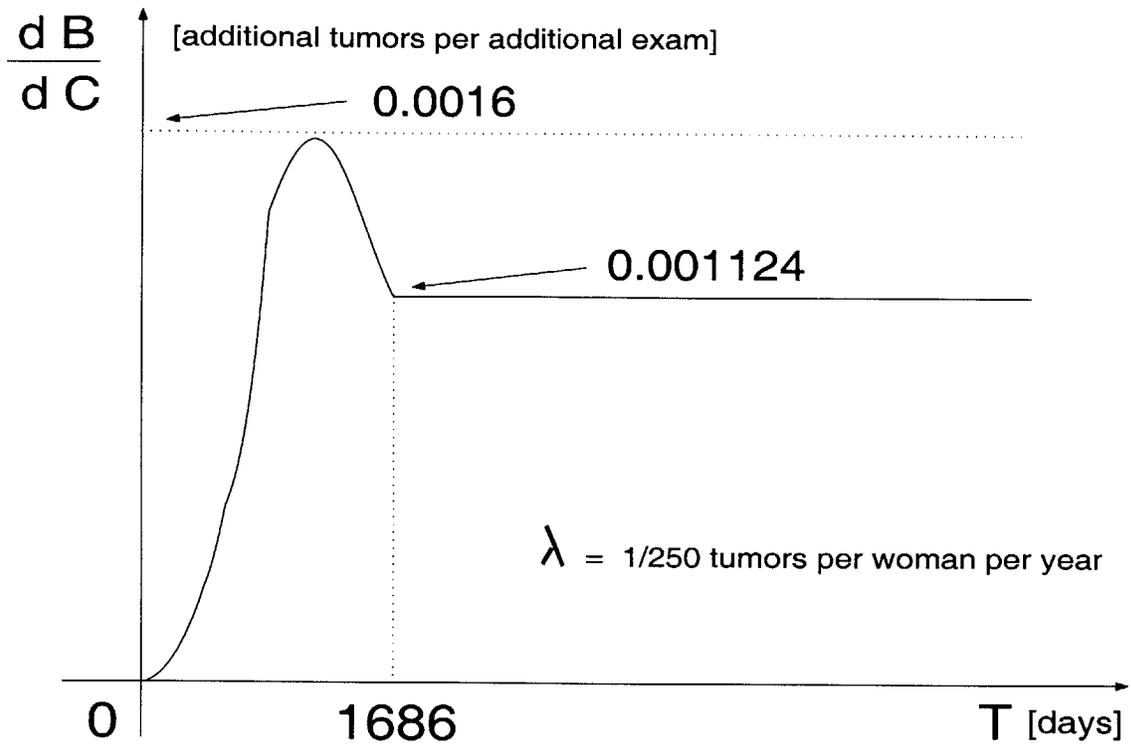
$P(T)$  is the probability that a single tumor is detected before metastasis.



$B(T)$  is the reduction in the number of patients with metastasis in population  $w$  per year.



$\frac{B(T)}{C(T)}$  is the reduction in the number of patients with metastasis in population  $w$  per individual exam.



$\frac{\partial B}{\partial C}(T)$  is the marginal benefit per unit cost at a particular interexamination interval  $T$ . It represents the expected increase in the reduction of the number of patients with metastasis in population  $w$  per additional examination per year.

## X Description of model M3

Again, we continue to modify the model one step at a time. In model M3 we change the representation of probability of detection by self-examination.

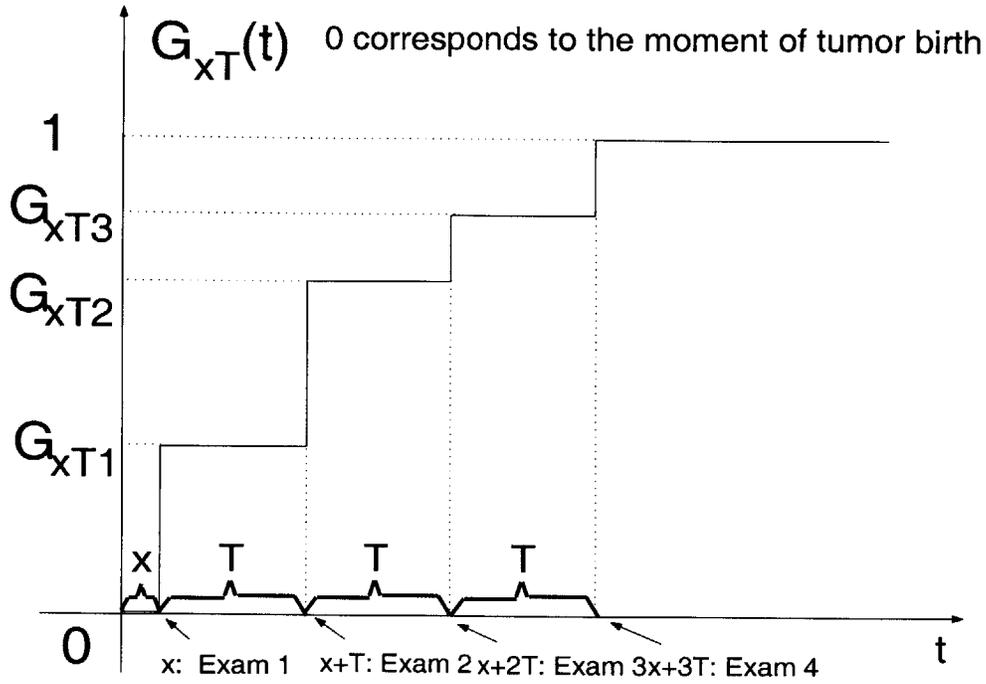
Probability of detection by self-examination,  $P_{d,self}(n(t))$ , is modeled as an arbitrary continuous monotonically non-decreasing function of  $n$ . We denote this probability function by  $s(n)$ . We can use the tumor growth law to express the probability of detection by mammography as a function of tumor age.

## XI Analysis of M3

The analysis in this section is very similar to that for Model M2, except for the handling of self-examination. We look at the probability that one random variable, the time of detection by mammography, is smaller than another random variable, the time of metastasis, or that one random variable, the time of detection by self-examination, is smaller than another random variable, the time of metastasis. Denote the time of metastasis by  $M$ , the time of detection by mammography by  $D_M$ , and the time of detection by self-examination by  $D_S$ . Then

$$P(T) = 1 - Pr \{M < D_M \cap M < D_S\} = 1 - Pr \{M < \min[D_M, D_S]\} \quad (86)$$

Similar to M2, we will deal with cumulative distribution functions. The first is  $F(t) = 1 - h(n(t))$ , same as in M2. Another is  $G(t)$ , similar to the one in M2, but not accounting for self-examination. In other words, the derivation of the new  $G(t)$  is based on  $P_{d,mamm}(n(t))$  as described in M2, not on  $d(n(t))$ , as described in M2. Similar to M2, the new  $G(t)$  takes into account that detection by mammography can only happen at discrete time intervals, and depends on the interscreening interval  $T$  and the tumor age at the first exam  $x$ . Below is the generic plot for  $G_{xT}(t)$ , the probability of detection at some  $\tau \leq t$  given the interscreening interval  $T$  and the tumor age at the first exam  $x$ .

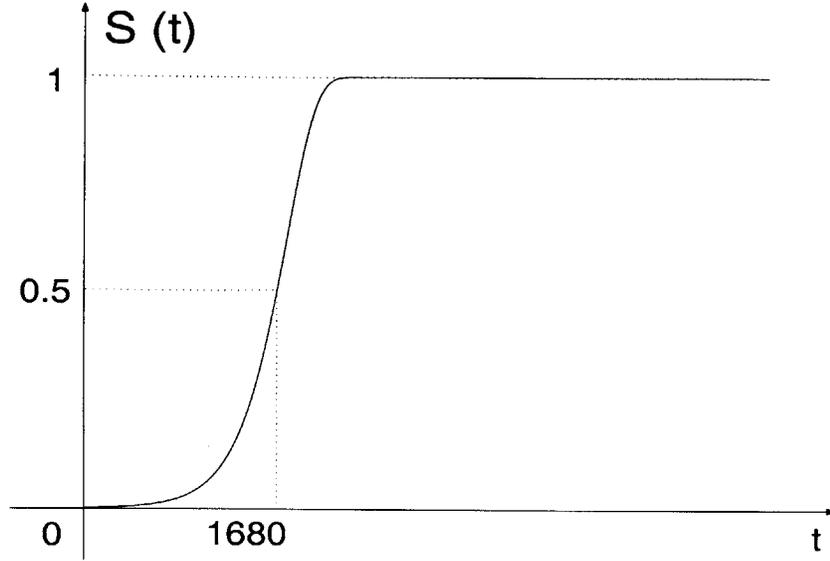


The third cumulative distribution function in this model is  $S(t)$ , corresponding to the probability of self-examination. We get this distribution function by fitting a curve into the data provided by Jim Michaelson [1].

$$S(D) = 1 - \frac{1}{e^{0.0022 \cdot D^{2.13}}}, \text{ where } D \text{ is the diameter of the tumor in millimeters} \quad (87)$$

$$= 1 - \frac{1}{e^{0.0022 \cdot (\sqrt[3]{e^{0.00533 t}})^{2.13}}}, \text{ where } t \text{ is the tumor age in days} \quad (88)$$

$$S(t) = 1 - \frac{1}{e^{0.0022 \cdot (\sqrt[3]{e^{0.00533 t}})^{2.13}}} \quad (89)$$



$$P(T) = 1 - Pr \{M < \min[D_M, D_S]\}$$

$$\text{Let } Z = \min[D_M, D_S].$$

$$\{Z > Z_0\} = \{D_M > Z_0\} \cap \{D_S > Z_0\}$$

$$(1 - F_Z(Z_0)) = (1 - F_{D_M}(Z_0)) \cdot (1 - F_{D_S}(Z_0))$$

$$\begin{aligned} F_Z(Z_0) &= 1 - (1 - F_{D_M}(Z_0)) \cdot (1 - F_{D_S}(Z_0)) & (90) \\ &= 1 - [1 - F_{D_M}(Z_0) - F_{D_S}(Z_0) + F_{D_M}(Z_0) \cdot F_{D_S}(Z_0)] \\ &= F_{D_M}(Z_0) + F_{D_S}(Z_0) - F_{D_M}(Z_0) \cdot F_{D_S}(Z_0) \end{aligned}$$

From this derivation we conclude that  $F_Z(t) = G(t) + S(t) - G(t) \cdot S(t)$ . We compute the probability that metastasis happens before detection by mammography or self-examination similarly to the way we did it for M2:

$$\begin{aligned} Pr \left\{ \begin{array}{l} \text{metastasis occurs} \\ \text{later than detection} \end{array} \right\} &= \int_0^\infty F'(t) F_Z(t) dt = \int_0^\infty F'(t) \cdot [G(t) + S(t) - G(t) \cdot S(t)] dt \\ &= \int_0^\infty F'(t) G(t) dt + \int_0^\infty F'(t) S(t) dt - \int_0^\infty F'(t) G(t) S(t) dt & (91) \end{aligned}$$

The first integral in the above expression corresponds to the expression for the probability of no metastasis before detection in the absence of self-examination as in M2. It also corresponds to the probability of no metastasis before detection in the absence of self-examination as in M3, since M3 differs from M2 only in the representation of the probability of detection by self-examination. The Matlab code for the numerical algorithm for computing the value of the first integral as a function of  $T$  is included in appendix I.2. This algorithm is similar to the algorithm used to compute probability of no metastasis before detection in the presence of self-examination.

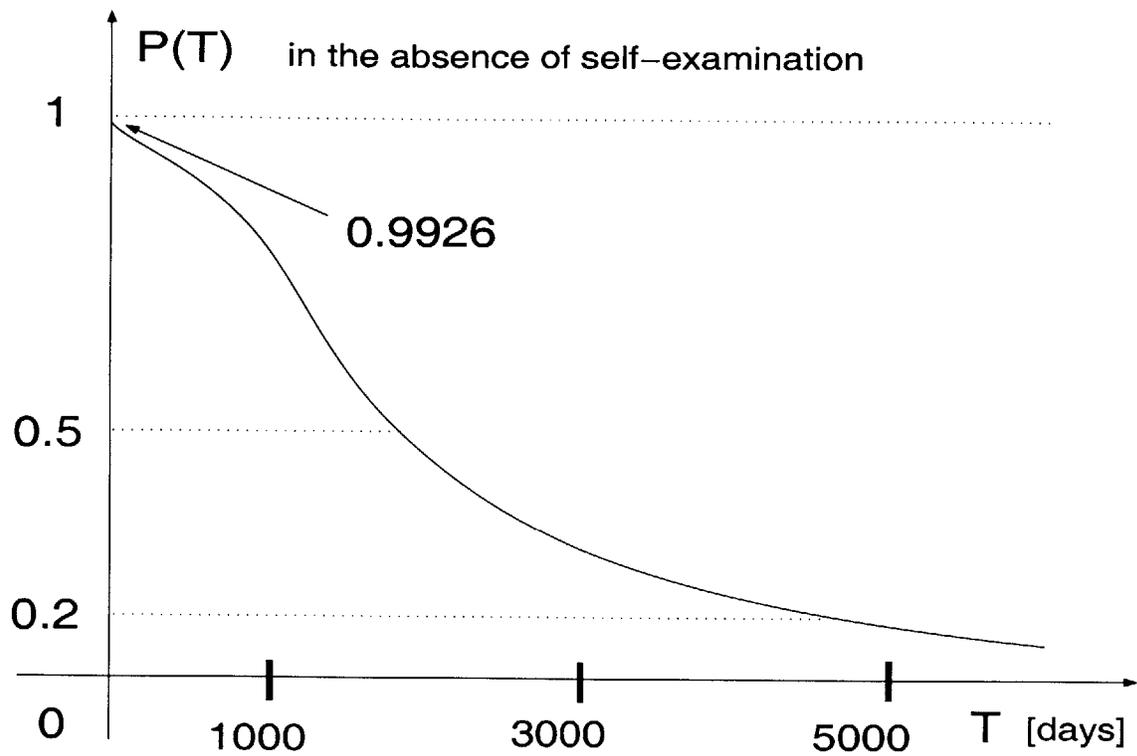
The second integral in the above expression corresponds to the probability of detection by self-examination when this probability is represented as in M3. We numerically compute this value. It turns out that  $\int_0^\infty F'(t) S(t) dt = 0.7896$ .

To evaluate the third integral we derive a new algorithm, similar to the algorithm for M2, and numerically compute the value of the intergral for each value of  $T$ . The Matlab code is included in appendix II.2. Then we add the three together to arrive at the values of  $P(T)$  for each value of  $T$  for M3.

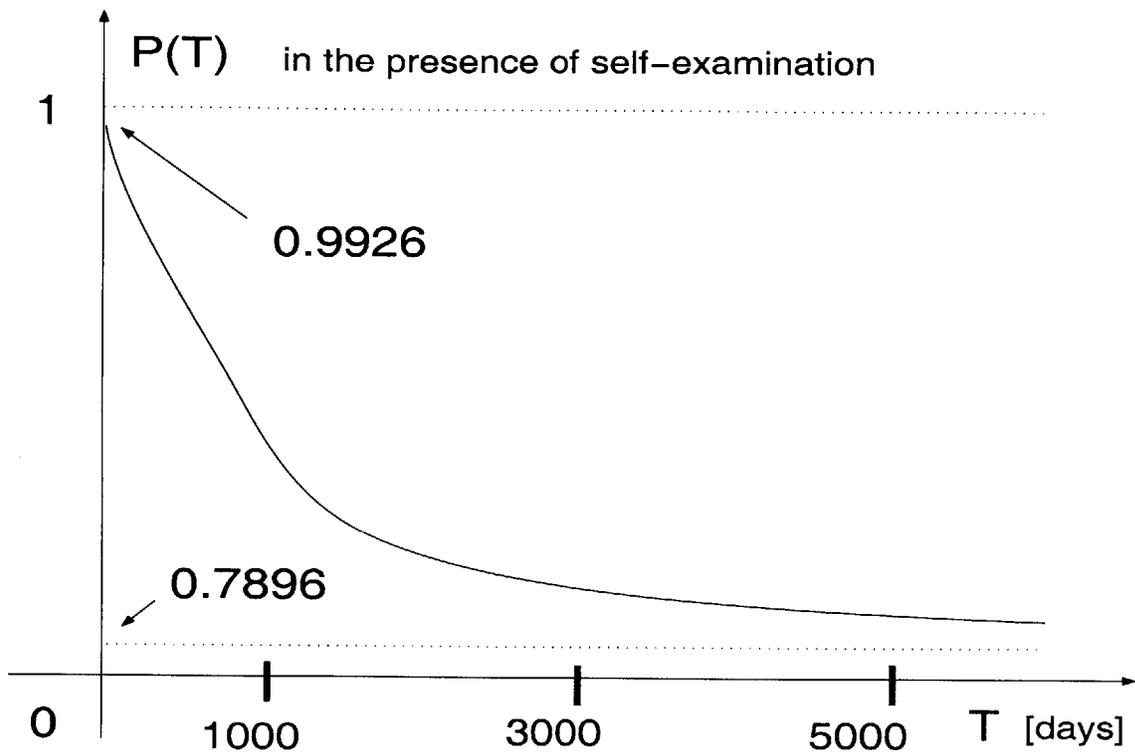
As in M2, we test the correctness of the algorithms by running them on the data with the assumptions of models M0, M1 and M2. The algorithms produce results that coincide with the results for M0 and M1 obtained analytically, and for the results for M2 obtained using the previous algorithm, giving some confidence that the algorithms are correct and reliable.

Similar to M2, we use  $P(T)$  to compute  $B(T)$ ,  $\frac{B(T)}{C(T)}$ , and  $\frac{\partial B}{\partial C}$ .

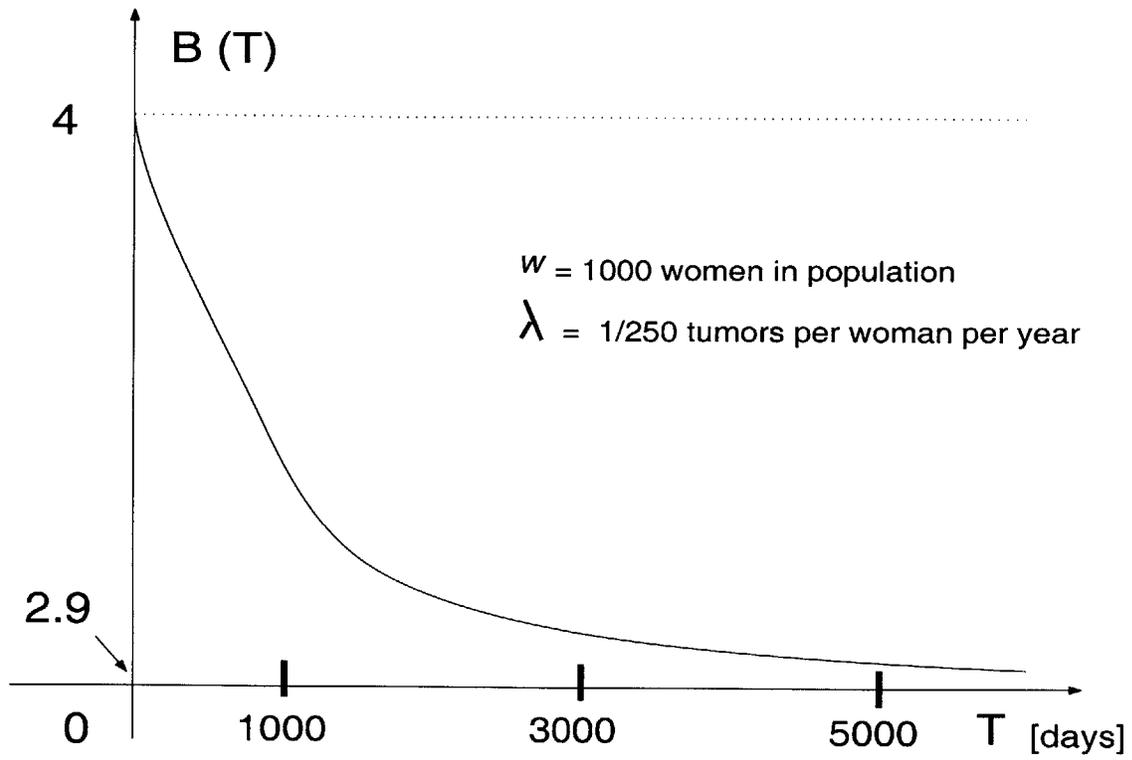
The graphs below illustrate the probability of no metastasis before detection in as a function of  $T$ , as well as  $B(T)$ ,  $\frac{B(T)}{C(T)}$  and  $\frac{\partial B}{\partial C}$  derived according to equations (83), (85) and (86), respectively.



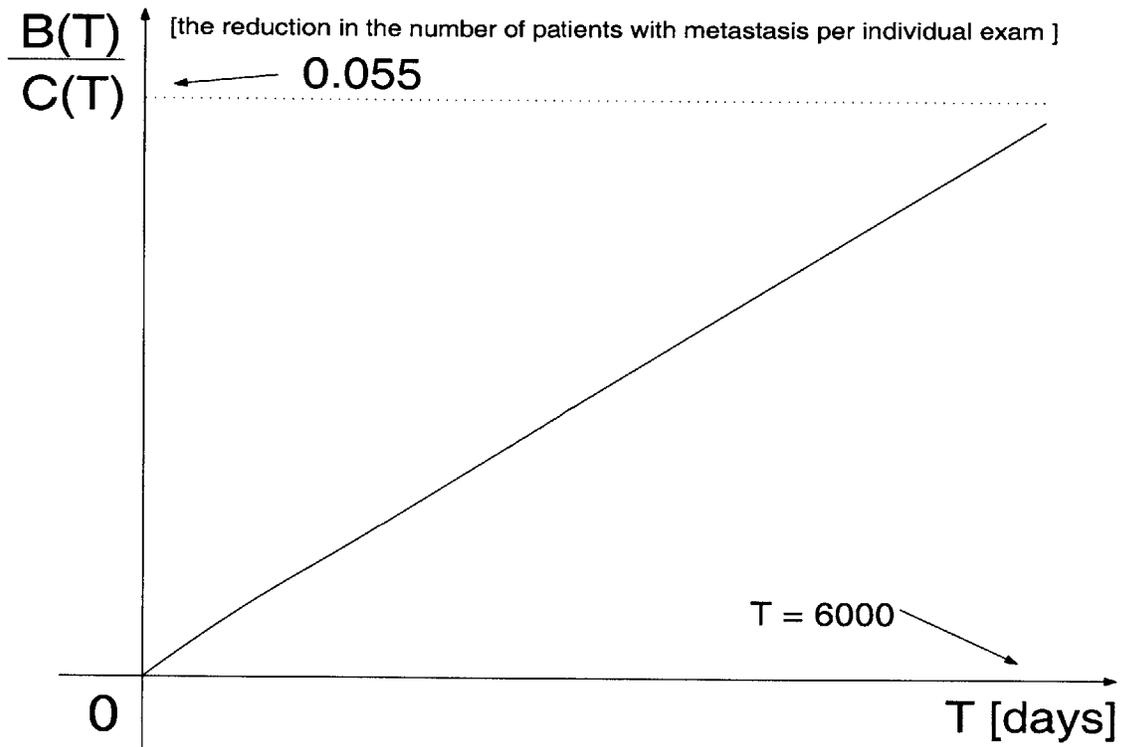
$P(T)$  is the probability that a single tumor is detected before metastasis. In the absence of self-examination, this probability is the same as it is in the model M2 in the absence of self-examination.



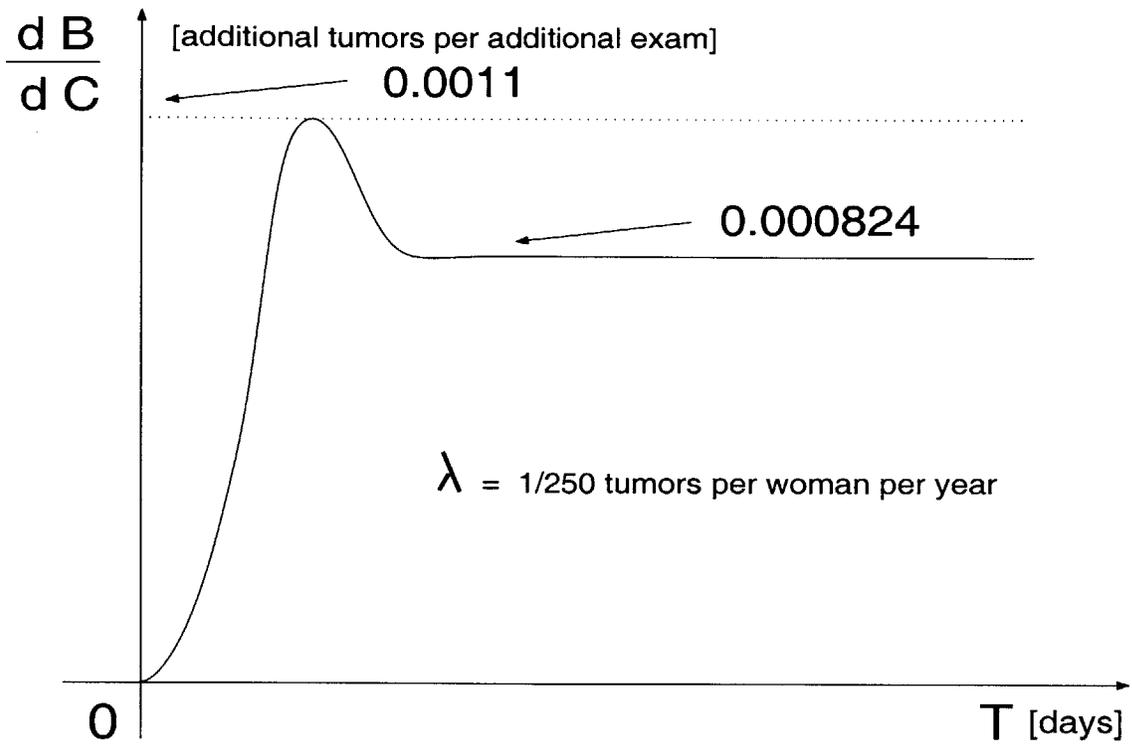
$P(T)$  is the probability that a single tumor is detected before metastasis.



$B(T)$  is the reduction in the number of patients with metastasis in population  $w$  per year.



$\frac{B(T)}{C(T)}$  is the reduction in the number of patients with metastasis in population  $w$  per individual exam.

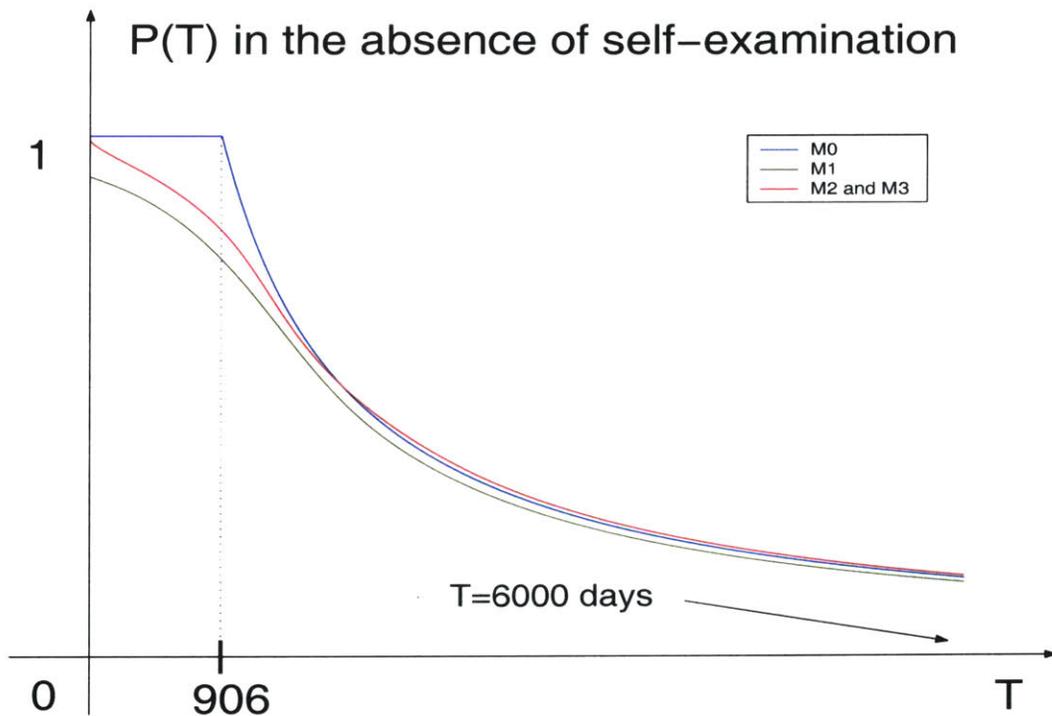


$\frac{\partial B}{\partial C}(T)$  is the marginal benefit per unit cost at a particular interexamination interval  $T$ . It represents the expected increase in the reduction of the number of patients with metastasis in population  $w$  per additional examination per year.

## XII Conclusions

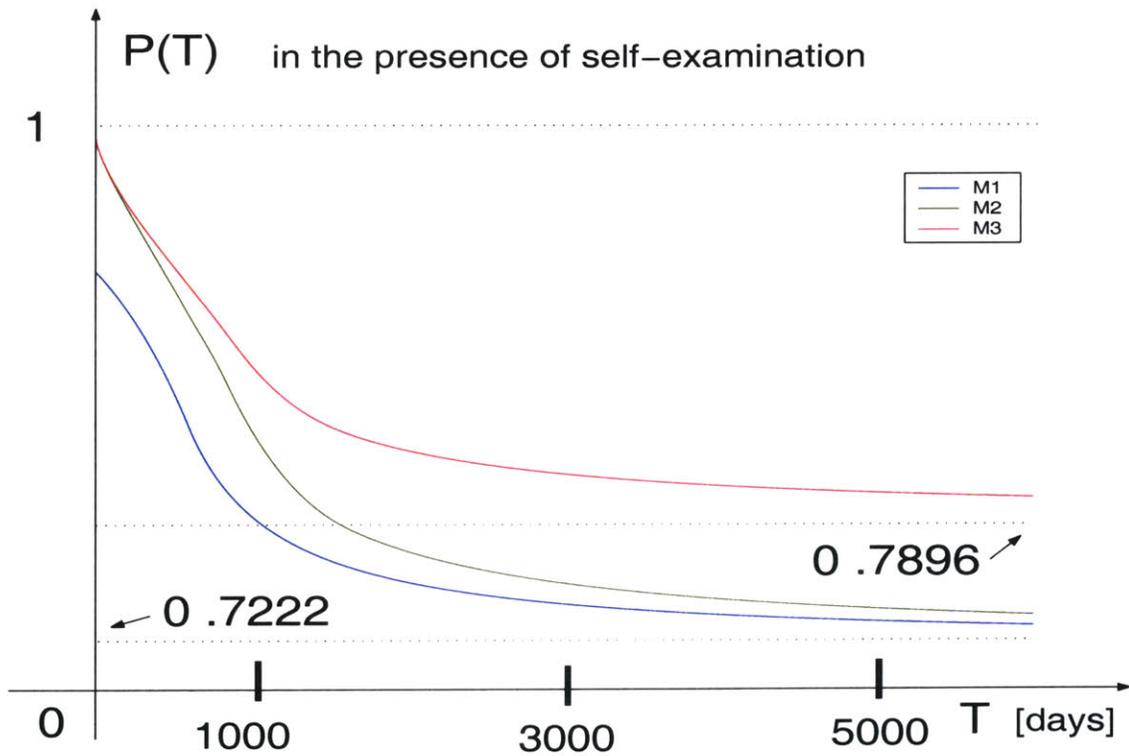
As we progress from model M0 to models M1, M2 and M3, our assumptions become more realistic and results start approximating reality significantly better. However, there is still many aspects in tumor occurrence, tumor growth, the probability of detection, the probability of metastasis etc. that remain to be accurately modelled before the results become reliable enough to be helpful for policymakers in arriving at the recommendations for interscreening interval and frequency of self-examination for women in different groups within the population.

In this section we compare the results from models M0 through M3, and analyse the differences between these results and the influence that more accurate modelling has on the results. We look at the plots of  $P(T)$  for two, three or four models simultaneously and discuss and analyze how these results compare.



The graph above compares the results for  $P(T)$  in the absence of self-examination for models M0 through M3. The results for M2 and M3 in the absence of self-examination are the same, since M2 and M3 only differ from each other in the representation of self-examination. The graph above shows that  $P(T)$  for M0 is greater than  $P(T)$  for M1, M2 and M3 for small values of  $T$ , but is smaller than  $P(T)$  for M2 and M3 for high values of  $T$ . The fact that  $P(T)_{M0} > P(T)_{M1, M2, M3}$  for small values of  $T$  is due to the representation of the probability of metastasis and the probability

of detection by mammography in M0 as step functions of the interscreening interval. Since the probability of metastasis in M0 is equal to zero for  $T \leq t_{met}$  and the probability of detection is equal to one for  $T \geq t_{d,mamm}$ , the probability of no metastasis before detection in this model is equal to 1 for small values of  $T \leq t_{met} - t_{d,mamm}$  corresponding to frequent examinations. In the absence of self-examination, the probability of no metastasis before detection starts falling very rapidly in M0 for values of  $T > 906$ , falls to approximately the level of  $P(T)$  for M1, M2 and M3 and continues falling at the same rate for large values of  $T$ . This is due to the fact that for large values of  $T$  the probability of metastasis is 1 for all the models, and the probability of detection by mammography is 1 or asymptotically approaches 1 for all models. The fact that  $P(T)_{M0} < P(T)_{M2,M3}$  for large values of  $T$  is possibly due to the specific choice of threshold  $n_{met}$  chosen for  $h(n)$  in M0.



The graph above compares the results for  $P(T)$  in the presence of self-examination. It is clear from the graph that self-examination has a significant effect on the probability of no metastasis before detection for models M1, M2 and M3. The graph shows that  $P(T)_{M1} \leq P(T)_{M2} \leq P(T)_{M3}$  for all values of the interscreening interval  $T$ . Since in all these three models the probability of metastasis is modelled as a continuous realistic function of tumor age, this relation holds due to the differences in representation of the probability detection by mammography and by self-examination

between the three models.

It appears reasonable that  $P(T)_{M1} < P(T)_{M2}$  for all values of  $T$ , since with the nonzero monotonically increasing with  $T$  probability of detection by mammography it becomes possible for the tumor to be detected at smaller sizes. The probability of detection at smaller sizes particularly matters for small values of  $T$ , which is reflected in the fact that the difference between  $P(T)_{M1}$  and  $P(T)_{M2}$  is greater for smaller values of  $T$ .

It is also reasonable that  $P(T)_{M2} \approx P(T)_{M3}$  for small values of  $T$ , and  $P(T)_{M2} < P(T)_{M3}$ . In M3 the probability of self-examination is represented as a continuous non-decreasing function of tumor size, and therefore the probability of detection by self-examination is greater in M3 than in M2. This, however, is much more significant for large values of  $T$ , since for small values of  $T$  most tumors get detected by mammography, not self-examination.

All  $B(T)$ ,  $\frac{B(T)}{C(T)}$  and  $\frac{\partial B}{\partial C}$  are functions of  $P(T)$ , and therefore their comparison is a direct consequence of the comparison of  $P(T)$  between different models, and can be deduced from the comparative analysis of  $P(T)$ .

As mentioned before, in the course of this research we started with building a very simple, overly coarse model M0 to gain intuition behind the basic aspects in tumor occurrence, growth, metastasis and detection. Later we modified the model adding realistic detail one step at a time. This approach has proved to be well suited for the problem, since starting with the basic model has allowed us to understand the basics well, and led us to modifying our definitions to their current form described in this thesis. Particularly, we had to change our definition of benefit twice in the course of this research, since the two previous definitions produced an undesirable anomaly in the results or made the analysis unnecessarily more complicated. It is likely that the anomaly in the results would have been obscured by other aspects of the model if we had not started with a set of very simple overly coarse assumptions. It is also likely that we would not have arrived at a simpler and better definition of benefit if our thinking remained obscured by the subtle aspects of the model.

While analysing the results of all the models, we have consistently relied on the analysis of the asymptotic behavior of the functions, looking at very small and large values of  $T$ . Such thinking has led us to doubt our initial assumptions of independence of exam outcomes, since for small values of  $T$  independence of exam outcomes implies a very high probability of detection after a large number of mammographic examinations, which can correspond to only a year or less of very frequent examinations. It is possible that later in the research such thinking will lead us to doubt other assumptions that have been previously made.

The necessity to give up previous definitions and assumptions has slowed down the pace of this research from the one originally expected. This slowdown, however, has been a very low cost for

the clarity of thinking attained, and for the approach to research that I have learnt in the course of working on the problem. Hopefully the later research in this field will be equally as stimulating and educationally valuable as it has been so far.

## XIII Notation

$B(T)$ : Benefit associated with the interscreening interval  $T$ , i.e. the expected number of tumors found in metastasis free patients per year.

$B_{mamm}(T)$ : Benefit from mammographic screenings associated with the interscreening interval  $T$ , i.e. the number of tumors found by means of mammography in metastasis free patients per year.

$B_{self}(T)$ : Benefit from self-examination associated with the interscreening interval  $T$ , i.e. the number of tumors found by means of self-examination in metastasis free patients per year.

$C(T)$ : Cost associated with the interscreening interval  $T$ .

$d$ : The interval between the time the tumor is detected and the time it is removed.

$D$ : The tumor diameter.

$D_M$ : The time of detection by mammography.

$D_S$ : The time of detection by self-examination.

$d(n)$ : Probability that a tumor of  $n$  cells is detected at a mammographic examination or by self-examination.

$F(D)$ : The fraction of patients surviving breast cancer as a function of tumor diameter  $D$ , a curve fit.

$F(t)$ : Probability that metastasis has occurred by time  $t$ .

$G(t)$ : Probability that detection by mammography has occurred by time  $t$ .

$G_{x1}, G_{x2}, etc.$ : Probability that detection by mammography occurs at the first mammographic exam in the tumor's lifetime, by the second mammographic exam in the tumor's lifetime, etc., given the tumor age at the first exam  $x$ .

$G_{xT}(t)$ : Probability that detection by mammography has occurred by time  $t$ , given the interexamination interval  $T$  and the tumor age at the first exam  $x$ .

$G_{xT1}, G_{xT2}, etc.$ : Probability that detection by mammography occurs at the first mammographic exam in the tumor's lifetime, by the second mammographic exam in the tumor's lifetime, etc., given the interexamination interval  $T$  and the tumor age at the first exam  $x$ .

$H(D)$ : Probability of detection by mammography as a function of tumor diameter, a curve fit.

$H(N)$ : Probability of detection by mammography as a function of the number of cells in the tumor, a curve fit.

$H(t)$ : Probability of detection by mammography as a function of the tumor age, a curve fit.

$h(n)$ : Probability that a tumor of  $n$  cells has not yet metastasized.

$M$ : The time of metastasis.

$n_m$ : The minimal size of the tumor when it is considered "having come into existence."

$n_{d,mamm}$ : The minimal size of the tumor detectable by a mammographic screening.

$n_{d,self}$ : The minimal size of the tumor detectable by a self-examination.

$n_{met}$ : The size at which the tumor metastasizes.

$N$ : The event that none of the tumors present in the patient have metastasized.

$N_{de}$ : Number of exams per year that detect one or more tumors.

$p_a$ : Probability that a woman has, right after a particular exam, one or more previously undetected tumors, all of size  $n_m$  or larger.

$p_b$ : Probability that a woman has, right before a particular exam, one or more previously undetected tumors, all of size  $n_m$  or larger.

$P(T)$ : Probability of no metastasis before detection for screening interval  $T$ .

$P_x(T)$ : Probability of no metastasis before detection for screening interval  $T$ , given the tumor age at the first exam  $x$ .

$P_{absent}$ : Probability that at the time of examination there are no present metastasized tumors not detected at this examination.

$P_{de}$ : Conditional probability that one or more tumors are detected at an exam, given that one or more previously undetected tumors are present.

$P_{d,mamm}(n)$ : Probability that a tumor of  $n$  cells is detected at a single mammographic exam.

$P_{d,self}(n)$ : Probability that a tumor of  $n$  cells is detected by self-examination.

$P_{incomplete}$ : Probability that part of the tumor is missed at the surgery.

$P_{self}$ : Probability that a single tumor is detected by self-examination during a given interexamination period, has not metastasized by the time of detection, and that none of the other present undetected tumors have metastasized.

$P_S$ : Probability that a life is saved at any given examination.

$r$ : Tumor growth constant.

$S(D)$ : Probability of detection by self-examination as a function of tumor diameter, a curve fit.

$S(t)$ : Probability that detection by self-examination has occurred by time  $t$ .

$t_1, t_2$  etc.: The times of examination.

$t_b$ : Birth time of the tumor, i.e.  $n(t_b) = n_m$ .

$t_{min}$ : The largest tumor age at which detection by mammography does not occur, with probability 1, if an exam is performed at the time the tumor is that age.

$t_x$ : The time of tumor metastasis.

$t_{detection}$ : The time when a tumor is detected by self-examination.

$T$ : The screening interval.

$t_{d,mamm}$ : The time it takes the tumor to grow from the minimal size  $n_m$  to the size detectable by mammography  $n_{d,mamm}$ .

$t_{d,self}$ : The time it takes the tumor to grow from the minimal size  $n_m$  to the size detectable by self-examination  $n_{d,self}$ .

$t_{met}$ : The time it takes the tumor to grow from the minimal size  $n_m$  to the size when it metastasizes  $n_{met}$ .

$\lambda$ : Tumor occurrence rate.

$w$ : Number of women in the population, taken to be 1000 in calculations.

$x$ : Tumor age at the first mammographic examination in its lifetime.

$Z$ : The time of detection by mammography or self-examination, whichever comes earlier.

# I Matlab Code

## I.1 Model M2

```
function [p] = m2 (d, h)
    % d is the probability of detection, as function of tumor age
    % h is the probability of metastasis, as function of tumor age
    % d and h have to have the same length, 6000
    % the function returns the probability of no metastasis before detection
    % as a function of T for values of T from 1 to 6000

    % loop through all possible values of T
for t=1:6000
        p(t) = 0;

        % loop through all possible values of tumor age at the first exam
        for i = 1:t
            % use s(i) to accumulate the value of p(t) for each possible age at the
            % first exam; initialize s(i) to 0.
            s(i) = 0;
            time = i;
            prev = 0;

            if time < 1686
                while time + t < 1686,
                    s(i) = s(i) + (d(time)*(1-prev) + prev)*(h(time + t) - h(time));
                    time = time+t;
                    prev = d(time)*(1-prev) + prev;
                end

                s(i) = s(i) + (d(time)*(1-prev) + prev)*(h(1686) - h(time));
            end

            s(i) = s(i) + 1 - h(1686);
            p(t) = p(t) + s(i);
        end
    end

    p(t) = p(t)/t;
end
```

## I.2 Model M3

```
function [p] = m3 (d, h)
    % d is the probability of detection, as function of tumor age
    % h is the probability of metastasis, as function of tumor age
    % d and h have to have the same length, 6000
    % the function returns the probability of no metastasis before detection
    % as a function of T for values of T from 1 to 6000

    % loop through all possible values of T
    for t=1:6000
        p(t) = 0;

        % loop through all possible values of tumor age at the first exam
        for i = 1:t
            % use s(i) to accumulate the value of p(t) for each possible age at the
            % first exam; initialize s(i) to 0.
            s(i) = 0;
            time = i;
            prev = 0;

            if time < 6000
                while time + t < 6000,
                    s(i) = s(i) + (d(time)*(1-prev) + prev)*(h(time + t) - h(time));
                    time = time+t;
                    prev = d(time)*(1-prev) + prev;
                end
                s(i) = s(i) + (d(time)*(1-prev)+prev)*(1 - h(time));
            end

            p(t) = p(t) + s(i);
        end
    end

    p(t) = p(t)/t;
end
```

```

function [p] = m3self (d, h)
    % d is the probability of detection, as function of tumor age
    % h is the integral of the product of the density of metastasis and the cumulative distribution
    %   of the detection by self-examination, as function of tumor age
    % d and h have to have the same length, 6000
    % the function returns the probability of no metastasis before detection
    % as a function of T for values of T from 1 to 6000

    % loop through all possible values of T
    for t=1:6000
        p(t) = 0;

        % loop through all possible values of tumor age at the first exam
        for i = 1:t
            % use s(i) to accumulate the value of p(t) for each possible age at the
            % first exam; initialize s(i) to 0.
            s(i) = 0;
            time = i;
            prev = 0;

            if time < 6000

                while time + t < 6000,
                    s(i) = s(i) + (d(time)*(1-prev) + prev)*(h(time + t) - h(time));
                    time = time+t;
                    prev = d(time)*(1-prev) + prev;
                end

                s(i) = s(i) + (d(time)*(1-prev) + prev)*(h(6000) - h(time));
            end

            p(t) = p(t) + s(i);
        end
    end

    p(t) = p(t)/t;
end

```

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