Working Paper

Stochastic Optimization of Screening Strategies for Preventing Irreversible Changes

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WP-94-124
December 1994

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Foreword

Considerable similarity exists between the types of processes involved in controlling human diseases, pollution of the environment, and failures in engineering systems. For example, screening for early detection of disease is similar to monitoring of the environment and to regular inspection schemes for engineering systems: all are directed towards detecting and reducing the risk of potentially irreversible changes. Understanding of such similarities may allow to use the same approaches in areas which seem remote at first glance.

This Working Paper reports the results of a collaborative project between IIASA (Methods of Decision Analysis project and the Risk Analysis and Policy project) and the Department of Public Health of the Erasmus University. The project, entitled "Optimization in non-linear dynamic stochastic systems with application in disease control" has been carried out at IIASA during the summer of 1993.

At the Department of Public Health, modelling of disease control started around 1977. A simulation model for cancer screening (MISCAN) has been developed and applied for analyzing large screening projects in Canada, the USA and in Europe. Predictions have been made of the results of screening, the effects, and its (cost-) effectiveness. The conclusions of these studies have had a significant impact on decision making about national screening programs in the Netherlands. The model is used in evaluation of screening in other countries (Australia, Germany, Italy, Spain) as well.

Cost-effectiveness analyses of disease control policies have become increasingly important. Early detection of the diseases by means of mass screening has proven to be effective in reducing mortality from breast cancer and cervical cancer. However, determining the costs and effects of a screening strategy is far from trivial because of the many interrelated factors involved. Fundamental characteristics of disease and screening processes are the uncertainty about the underlying mechanisms that cannot be observed directly, and the occurrence of abrupt changes both as part of the natural history of the disease (for example the risk of dying from the disease) and as caused by medical interventions. One of the goals of cost-effectiveness analyses of screening for disease is to find screening strategies that are optimal for a certain criterion. Examples of criteria are mortality reduction achieved, life years gained, possibly in relation the additional costs of screening. Realistic models describing the disease process and interventions require stochastic simulation techniques, which however provide only random observations of the possible outcomes. In this situation, optimization of the intervention strategies leads to a methodologically challenging task to design appropriate search procedures.

The aim of this collaborative paper is to investigate such optimization procedures for screening strategies for systems involving risks and irreversible changes. Although the paper concentrates on models of screening for disease, the approach is rather general and can be useful for other applications. In disease control, optimization methods have thus far only been applied for rather simple models. Advanced optimization methods have the advantage that realistic models can be used, leading to well-founded recommendations that are based on explicit and extensive integrated risk and uncertainty analysis. This will strengthen the role of modelling as an aid in decision making for disease control.

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1. INTRODUCTION

A fundamental characteristic of such processes as diseases, environmental degradation or deterioration of the engineering systems is the possibility of occurrence of abrupt transitions when certain threshold levels are exceeded. Such a "threshold" may reflect either the essential nature of processes under consideration or will only be an approximation to the reality valid in the lack of complete information about gradual changes. For example, accumulation of pollutants may lead to almost irreversible environmental changes ("time bomb" phenomena). Similarly, long time exposure of human individuals to risk factors may lead to disease and premature death, for example smoking and lung cancer. A failure of engineering equipment can be compared with the transition from state "no disease" to "disease" in a human being.

In the cancer screening model considered in this paper, the system under study is a human individual, who will normally be in the state "no cancer". A cancer process may develop which is described by a (age-dependent) Semi-Markov process with terminal states (death from cancer, death from other causes). Regular inspection of this system (cancer screening) may result in early detection of abnormalities, and subsequent intervention will lower the risk of further development of the cancer and death. Because of the general formulation of the model, the proposed optimization methods may also be useful for other applications.

During the last decades considerable efforts have been devoted to the development of the simulation tools for inherently stochastic systems involving chains of discrete events - discrete event system (DES), aiming at applications to large scale systems such as telecommunication networks, manufacturing, material flow, and queuing systems (see for references, for example Ermoliev & Gaivoronski [1992], Gaivoronski [1992], Ho & Cao [1991], Glasserman [1991]. These modelling tools require appropriate optimization techniques and stochastic optimization seems to be a natural approach in this respect.

A stochastic simulation model will always give some amount of random variation in the outcomes for a given decision. Still, it can be used to compare different policy options that are specified explicitly as input to the model. Because of the random nature of the outcomes, the search of optimal decisions in this situation is similar to the testing of hypothesis, to automation learning problems, and to the so-called multi-arms bandit problems on the choice of policies when benefits are uncertain (Gittins [1989]).

When a stochastic simulation model includes a rich set of the decision variables, for example given implicitly by a number of "feasibility constraints", the enumerative evaluation of desirable decisions becomes tremendously difficult. Stochastic optimization procedures are designed to deal with infinite sets of possible decisions and allow to bypass these difficulties.

In this paper we use this approach to develop an optimal screening policy for a particular disease process - cervical cancer. Screening or early detection is also known as "secondary prevention" to distinguish it from the other main types of disease control: primary prevention (reduction of risk factors, e.g., smoking or contaminated drinking water) and treatment of patients that have been diagnosed on basis of symptoms. See Morrison [1992] and Miller *et al.* [1991] for an overview of issues, problems, and methods in cancer screening. Cervical cancer is one of the few cancer types for which early detection, by means of the Pap-smear, has been shown to be effective in reducing the incidence and mortality, especially in the younger age groups which have been screened intensively. Without mass screening of the female population, the annual number of deaths would probably have been more than twice the present level. Mass screening with the Pap-smear started already around 1950 in parts of Northern America (e.g., British Columbia). In most (West-)European countries it was only introduced on a large scale some 15-20 years later.

The screening test not only detects the invasive form of cervical cancer in an early stage, but is especially effective since it will identify pre-invasive stages. Treatment of these stages results in virtually 100% cure, whereas early detection of (macro-)invasive stages still incurs a non-negligible risk of dying from the disease. A complication is that a proportion of the pre-invasive lesions do not progress (become invasive), but regress to normal spontaneously. Early detection in these cases leads to unnecessary treatment, since there is as yet no method to discriminate between progressive and regressive lesions.

From a Public Health point of view, the most important effect of cervical cancer screening is the prevention of mortality and the associated life-years lost. Additional favourable effects are the prevention of metastatic and

terminal stages of cancer, the reduction of the incidence of invasive cancers (because of detection and treatment of pre-invasive lesions), and a shift towards less severe treatment of the cases detected.

The main adverse effect of screening is probably the already-mentioned unnecessary treatment of non-progressive lesions. Early diagnosis of invasive cancer can also be regarded as an adverse effect, because of the additional "lead-time" in which a woman knows that she has cancer. This is especially true for women for which screening has no positive effect, either because they would not have died from the disease anyway, or because death from cervical cancer is not prevented despite early detection and treatment.

The main costs involved are the cost of the screening: the invitation, examination and cytologic assessment of the smear. Medical costs of diagnosis and primary and additional treatment will change, but the changes will to some extent cancel each other out. The magnitude of the resulting change in cost of diagnosis and treatment is small compared to the screening costs. Therefore, the costs of a cervical cancer screening program are approximately proportional to the number of screening examinations, see (Koopmanschap *et al.*[1990]), and the same is true for the adverse effects of screening (van Ballegooijen *et al.*[1992]).

The simulation model MISCAN (Habbema *et al.*[1984]), developed at the Department of Public Health, Erasmus University Rotterdam, is used for stochastic evaluation of the disease process and the intervention by screening. MISCAN is based on simulation of discrete events that are related to a person and to the disease process in a person, and to the screening examinations and the resulting impact on the disease history.

The MISCAN group is represented in the evaluation boards for both breast cancer and cervical cancer screening in The Netherlands. These boards analyze the results of the screening activities and, if necessary, make recommendations about policy adaptations. One of the key elements in a screening policy is the choice of the screening strategy, i.e. the ages at which women are to be invited for screening. For cervical cancer, striking differences between policies can be found in starting age, interval between tests, and upper age for screening.

Several factors determine the number of life years that are gained by a screening strategy. The number of cases detected by screening depends on the age-specific incidence and prevalence of the screen-detectable stages, and on the time since preceding screening tests. The number of life years gained when a cancer is detected in a person is related to the age of the person and the stage of the disease: younger persons have a higher life-expectancy, and will therefore loose more life years when they would die from the cancer. But age has also a more indirect effect since it influences the course of the cancer.

Screening may also fail to prevent death: the screen-detectable stage may develop completely between tests, or before the first or after the last screening test. Also, the screen-detectable stage may not be detected because of non-participation or because of a false negative test result, or the early detection and treatment may not help to prevent a lethal course of the disease.

In section 2 microsimulation and the optimization problem for cancer screening are introduced. In section 3 different approaches for stochastic optimization are presented and discussed. Section 4 describes the problems arising in application of the Stochastic Quasi Gradient approach to cancer screening, for the case of one screening examination. Section 5 describes the extension to more than one screening test. In section 6 the implementation and quantification for the cervical cancer screening model, and preliminary optimization results are presented. Section 7 summarizes the findings and discusses extensions to the model and the objective function, and applications for other types of disease control problems.

2. MICROSIMULATION AND OPTIMIZATION

The cervical cancer screening model used is an extended version of a model that was used to analyze screening programs, see Oortmarssen & Habbema [1991,1992], and covers all key aspects of the screening problem, see Figure 1.

The model consists of six disease stages, and three additional stages: death from cervical cancer, death from other causes and hysterectomy (UTERUS EXTIRPATED) for other reasons than cervical cancer. It is assumed that the risk of death from other causes or hysterectomy for other reasons than cervical cancer is independent from the risk of cervical cancer.

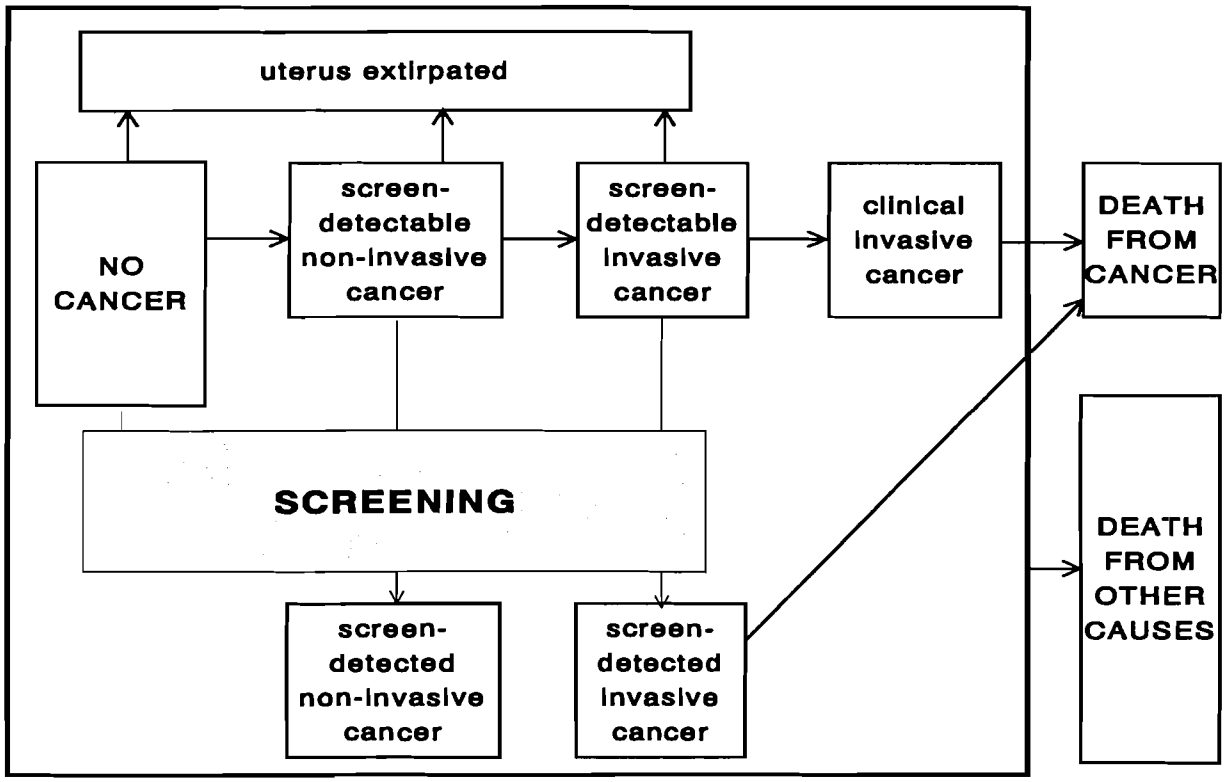

Figure 1 Simplified model of cervical cancer screening: states and transitions.

From the initial stage NO CERVICAL CANCER, transitions to the stage NON-INVASIVE CERVICAL CANCER (which includes Dysplasia and Carcinoma in Situ) occur at two different rates, for younger and for older women, respectively. The duration of this stage is governed by a probability distribution function which is characterized by the mean duration (estimated value: 12 years) and the variability of this duration which is considerable: 20% of new progressive lesions will enter the stage PRE-CLINICAL INVASIVE CANCER within 5 years. The estimated probability of spontaneous regression is 84% for younger women and 40% for older women. We will however neglect this possibility of regression (transition from PREINVASIVE CANCER back to NO CANCER) in the present paper, since it does not influence the effect of screening on mortality. Only progressive case-histories will be taken into consideration.

In the absence of screening, all invasive cancers will eventually be diagnosed clinically (stage CLINICAL INVASIVE CERVICAL CANCER). The duration of screen-detectable PRE-CLINICAL INVASIVE cancers is assumed to be constant, and estimated to be 4 years. Thus, the total average duration of (progressive) screen-detectable stages is between 14 and 20 years. The probability of detecting a pre-clinical lesion by a Pap-smear is estimated to be 80% in PRE-INVASIVE CERVICAL CANCER and 90% in PRE-CLINICAL INVASIVE CANCER. Screening participants constitute a group which has below-average risk of developing cervical cancer; the estimated relative risk is 74%.

We will first describe the steps of the brute-force microsimulation approach which corresponds to current MISCAN practice. The performance (for example, the number of life years gained) of a screening

strategy is estimated as follows. Let x be a screening strategy consisting of n ages at which women are invited for screening: $x=x_1,x_2,..,x_n$, $x_{min}<x_1<x_2<..<x_n<x_{max}$. Persons who reach one of these ages will be invited to attend the screening examination. Participants with an early stage of the disease have a probability that the disease is detected, which may lead to prevention of death from the disease. The boundary ages x_{min} and x_{max} represent ages for which screening is no longer worth consideration. In case of cervical cancer, we could for example take x_{min}=15 and x_{max}=80.

A life history ω_s from the model depicted is represented by events (transitions in Figure 1) and corresponding variables (shown in Figure 2) which can be categorized into three groups:

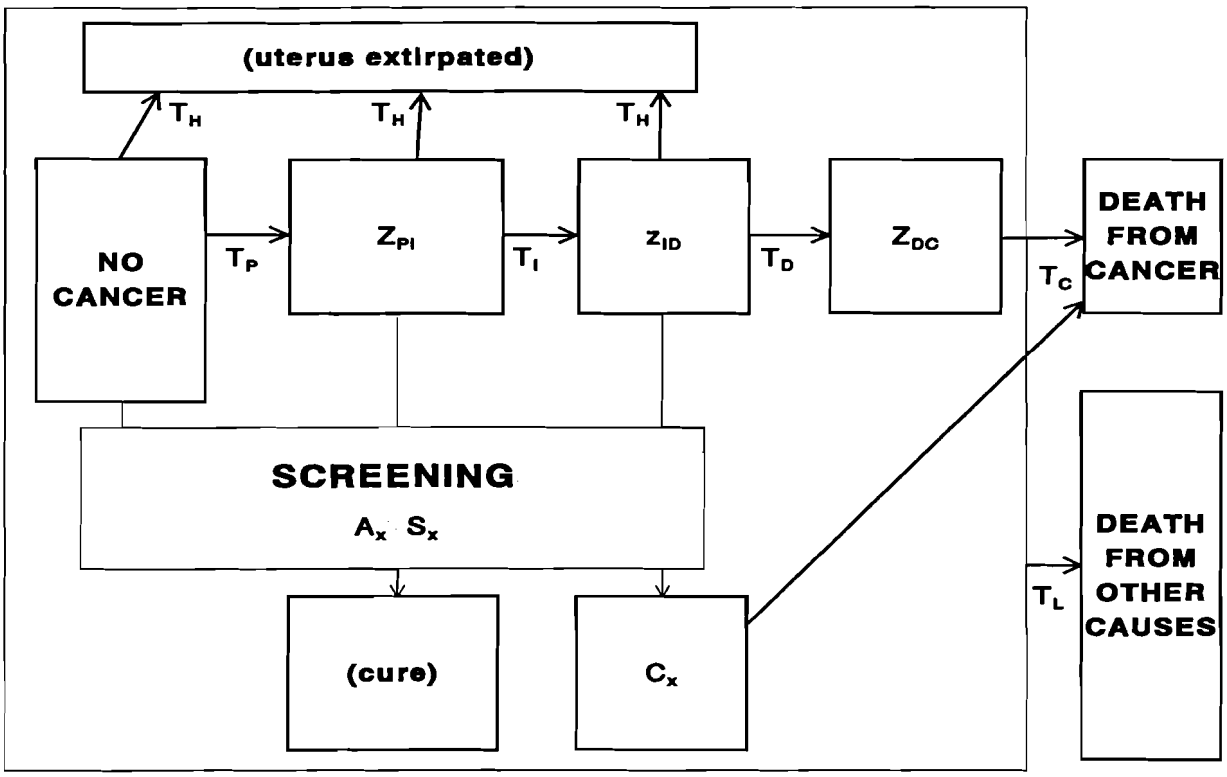

Figure 2 Simplified model of cervical cancer screening: variables.

GROUP 1: screen-detectable disease stages

T_P - age at entry in screen-detectable progressive non-invasive stage

T_I - age at entry in screen-detectable invasive stage, $T_I = T_P + Z_{PI}$.

T_D - age at clinical diagnosis of cancer, $T_D = T_I + Z_{ID} = T_P + Z_{PI} + Z_{ID}$.

Z_{PI} and Z_{ID} denote the duration of the screen-detectable preinvasive and invasive stages, respectively. It is assumed that T_P, Z_{PI}, and Z_{ID} are independent non-negative variables, with p.d.f's $F_P(t) = Pr\{T_P \le t\}$, $F_{PI}(z) = Pr\{Z_{PI} \le z\}$ and $F_{ID}(z) = Pr\{Z_{ID} \le z\}$.

GROUP 2: clinical course of the disease

T_C - age at death from cervical cancer, $T_C = T_D + Z_{DC}$. Z_{DC} is the survival time following clinical diagnosis, and may be "very" long which means that the cancer is cured. The p.d.f. of the survival is $F_{DC}(z) = Pr\{Z_{DC} \leq z\}$

T_L - age at death from other causes, independent from T_P.T_C, with p.d.f. $M_L(t_L) = Pr\{T_L \leq t_L\}$.

T_H - age at which a hysterectomy (uterus extirpation) is performed for other reasons than cervical cancer. Women who have had a hysterectomy are no longer at risk for developing cervical cancer. The p.d.f *is* $M_H(t_H) = PR\{T_H \leq t_H\}$, and T_H is assumed to be independent from T_P.T_C and from T_L. For simplicity, we assume that the cervical cancer disease process is fully interrupted when a hysterectomy is performed before the clinical diagnosis, i.e. when $T_H < T_D$.

GROUP 3: events related to screening test at age x:

A - participation at screening (1=Yes,0=No}

S - true positive (1) or false negative (0) result of screening test in screen-detectable stage

C - cure (1) or no effect (0) of early treatment. Detection of a non-invasive cancer will always imply cure.

It is assumed that screening can have two effects: no change in the time of death T_C, or complete cure. If we consider the number of life years gained as the criterion for judging the effect of screening, then the sample performance function $g(x,\omega)$ for a given sample ω can have two values: 0 or T_L-T_C. For the case of a single screening test (n=1) at age x, the performance function has the following structure:

$$g(x,\omega)=\begin{cases} T_L - T_C & \text{if } (T_L > T_C) \wedge (T_H > T_C) \wedge (A=1) \wedge (S=1) \wedge \\ & \quad ((T_P \leq x < T_I) \vee (T_I \leq x < T_D) \wedge (C=1)) \\ 0 & \text{elsewhere} \end{cases} \tag{1}$$

This is a discontinuous step-wise function, and the derivative with respect to x is equal to 0 almost everywhere. The changes in the performance occur only at the points of the discontinuities, where it changes from 0 to T_L-T_C or vice versa.

Instead of considering only the number of life years gained, the performance criterion $g(x,\omega)$ could also integrate several other desirable and adverse effects, and may include many components. In case of cancer screening, an example of such a multi-component performance measure is the QALY (quality adjusted life years), see [de Haes et al 1991].

A further complication arises when costs are taken into account in the performance function, and the optimization criterion becomes (quality adjusted) life year gained per unit cost, i.e. the ratio of health effects $g(x,\omega)$ and costs $h(x,\omega)$. If the costs are only made up of the cost h_E of the screening examination, then the sample cost function for a single screening at age x is:

$$h(x,\omega)=\begin{cases} h_E & \text{if } (x < T_L) \wedge (x < T_H) \wedge (x < T_D) \wedge (A=1) \\ 0 & \text{elsewhere} \end{cases} \tag{2}$$

First, we will concentrate on the sample performance function (1) representing the number of life years gained. In contrast to this sample performance function, the *expected* performance function $G(x)$ of strategy x is obtained by integrating over the effect of all possible sample histories ω:

$$G(x)=Eg(x,\omega)=\int g(x,\omega)P(x,d\omega) \tag{3}$$

where $g(x,\omega)$ is a sample performance function of a random life-history ω generated by simulation, and $P(x,d\omega)$ is the corresponding probability which may depend on x as it is in the case of the sample performance function defined by the equation (1). Analytical, explicit formulae for $G(x)$ will in general not be available for realistic models.

Once the sample life history ω is known, the function $g(x,\omega)$ can be expressed explicitly. In case of more than one screening, this will involve a collection of simple recursive formulas. Each simulated history provides the value of $g(x,\omega)$ for some fixed (x,ω). The optimization problem is to maximize the averaged performance criterion (3) on the set $\mathbf{X}\in\mathbf{R}^n$ of admissible control strategies

$$x_{min}\le x_1\le x_2\le\ldots\le x_n\le x_{max} \tag{4}$$

In a more general problem there may be additional constraints (for example available budget or equipment) in addition to the requirement (4).

3. STOCHASTIC OPTIMIZATION APPROACH

As it was mentioned above, the main difficulty in optimizing the performance function $G(x)$ is the lack of exact information on $G(x)$. Each simulation run provides only random values $g(x,\omega)$ of $G(x)$, which can be used in the search of desirable policies. This is typically a situation in which stochastic optimization techniques can be applied, see Ermoliev & Wets[1988] for a general introduction on stochastic optimization.

We will sketch three possibilities for developing an optimization procedure: (a) enumeration of a finite number of strategies; (b) explicit approximation of $G(x)$; (b) use of Stochastic Quasi-Gradient methods.

(a) Enumeration of a finite number of strategies.

In some problems, it is possible to restrict the attention to a finite number of K strategies:

$$x^{(k)}=(x_1^{(k)},\ldots,x_n^{(k)}), \qquad k=1,\ldots,K \tag{5}$$

satisfying feasibility constraints (4). The search of the strategy k* maximizing the expected performance

$$\begin{aligned} G^{(k^*)}&=\max_{1\le k\le K} G^{(k)}, \\ G^{(k)}&=Eg(x^{(k)},\omega) \end{aligned} \tag{6}$$

on the basis of the random samples $g(x^{(k)},\omega)$ is equivalent to the well known hypotheses testing, the multi-armed bandit, and automaton learning problems, see for example Gittins [1989]. Such an approach is possible only for simple feasibility constraints and a good priory intuition about the structure of optimal policy.

(b) Explicit approximation of $G(x)$.

An approximation of $G(x)$ can be derived either in a neighbourhood of the current solution or uniformly in the feasible set (i.e., the set of all relevant strategies). Conventional deterministic optimization techniques can be used to optimize the approximative function.

One family of such procedures is known as Response Surface Methods. In these methods, the function $G(x)$ is approximated by a quadratic function $Q(x)$ in the neighbourhood of a current solution x by using random values $g(x,\omega)$. Then, standard optimization techniques are used for $Q(x)$ to produce a new solution. Again, random values $g(x,\omega)$ are generated for the new x, leading to a new response surface $Q(x)$ and so on. This approach requires estimation and updating of the coefficients of $Q(x)$ at each step of the search procedure,which may become very time consuming when the number of decision variables (screening ages) increases.

An alternative approximation method is to use an approximation of $G(x)$ in the whole feasible set. The most important approximation of $G(x)$ is defined as the sample mean which is obtained by generating N life histories ω_i, $i=1,..,N$, and calculating the mean value of the sample performance $g(x,\omega)$:

$$G^N(x) = \frac{1}{N} \sum_{i=1}^{N} g(x,\omega_i) \tag{7}$$

Thus, instead of the exact value of the performance $G(x)$, a statistical estimate based on a (large) sample of generated life-histories $g(x,\omega)$ is used. For optimization of the function $G^N(x)$ a conventional deterministic procedure may be used, provided that $G^N(x)$ has a well defined analytical structure and that the probability $P(x,d\omega)$ does not depend on x.

However, as shown in equation (1), this is not the case in the problem under consideration in which $g(x,\omega)$ is piece-wise constant, leading to a highly discontinuous function $G^N(x)$, $N\to\infty$, with derivatives equal to 0 almost everywhere.

Despite the discontinuity of $g(.,\omega)$ the expected performance function $G(x)$ may be smooth and continuously differentiable, and it may well be possible to remove discontinuities in the sample performance function $g(x,\omega)$ by using conditional expectations. Suppose A is a set of events such that it is possible to take the conditional expectation:

$$\bar{g}(x,\omega) = E\left[g(x,\omega)|A\right], \qquad G(x) = E\left[\bar{g}(x,\omega)\right] \tag{8}$$

After taking the expectation, the sample performance $\bar{g}(x,\omega)$ may become continuously differentiable and the corresponding probability distribution $\bar{P}(x,d\omega)$ may become independent of x. Now $\bar{g}(x,\omega)$ can be used instead of $g(x,\omega)$, and conventional optimization techniques are applicable for maximizing $G^N(x)$. A further difficulty in using $G^N(x)$ is that it may often have local solutions even if $G(x)$ has only a global optimum. In addition, construction of $G^N(x)$ may be a very tedious task, as it is in the screening problem.

(c) Stochastic Quasi-Gradient (SQG) methods.

The most important information required in the optimization is the direction in which the function $G(x)$ increases. The SQG methods are based on estimation of gradients of $G(x)$ directly, without the approximation

of $G(x)$ by an explicit function of x such as $Q(x)$ or $G^N(x)$. In the SQG approach, a sequence of approximative solutions x^0, x^1, ... is generated by using at each step s=0,1,2,... random vectors ξ^s such that in a certain sense

$$\left| E[\xi^s | x^0,...,x^s] - G_x(x^s) \right| \to 0, \quad s\to\infty \tag{9}$$

where $G_x(x^s)$ is the gradient (or generalized gradient if $G(x)$ is not a continuously differentiable function) of $G(x)$. An example of such a vector ξ^s for a given sample life histories ω and υ is:

$$\xi^s = \frac{2}{3} \frac{g(x^s + \Delta_s h^s, \omega^s) - g(x^s, \upsilon^s)}{\Delta_s} h^s \tag{10}$$

where x^s is the current approximate solution, Δ_s is a step multiplier in direction h^s, which is the random vector with components that are independently and uniformly distributed on [-1,1], and ω^s and υ^s denote samples from the probability distribution $P(x,d\omega)$ for $x = x^s + \Delta_s h^s$ and $x = x^s$, respectively. In this example, only the finite-difference approximation in the random direction h^s is calculated. Another possibility is to use finite-difference approximation (central or forward) in all n directions. If function $G(x)$ has continuous derivatives then, for ξ^s defined by (10):

$$\left\| E[\xi^s | x^s] - G_x(x^s) \right\| = o(\Delta_s) \tag{11}$$

despite of possible discontinuity of the sample performance $g(x,\omega)$. This estimate does not require a well defined structure of $g(x,\omega)$. With a slight modification, this type of stochastic quasi-gradient can be used even for discontinuous functions $G(x)$ (see Ermoliev, Norkin and Wets[1994]). When the structure of $\overline{g}(.,\omega)$ as defined in (8) is known, then analytical derivation of the stochastic gradients $\overline{g}_x(x,\omega)$ is possible. Although it requires (substantial) additional effort, it is advantageous since it avoids the bias which occurs when gradient is estimated by finite difference approximation.

From equation (1) it can be seen that in optimizing cancer screening strategies the sample performance function $g(x,\omega)$ is highly discontinuous. Additional analysis is required to smooth $g(x,\omega)$ before it can be used to find $g_x(x,\omega)$.

In this paper we explore this possibility to design a SQG procedure for optimizing cancer screening strategies. In other words, in order to remove discontinuities and calculate $\overline{g}_x(.,\omega)$ we replace some of the micro-simulated processes by macro simulated processes (conditional expectations). This also reduces the variance of the stochastic gradients, and in many cases it decreases the computer time required to find an appropriate solution.

The general structure of proposed SQG procedure is the following : A sequence of solutions x^0, x^1,...,x^s,... is generated that converges with probability 1 to an optimal solution of the original problem. It may be sufficient to sample only one history ω at each step. The sequence is produced according to the rule

$$x^{s+1} = \Pi_X(x^s - \rho_s \xi^s) \tag{12}$$

where Π_X denotes the projection operator on the set $\mathbf{X}$, ρ_s is a step size and ξ^s is a stochastic gradient defined by formulas for $\overline{g}_x(.,\omega)$ that will be derived in next sections. Development of an appropriate estimator $\overline{g}_x(.,\omega)$ is a critically important task which may often involve probabilistic analysis and non-smooth optimization techniques.

When the criterion for comparing policies is cost-effectiveness rather than effectiveness, then the performance function can be modified by taking the ratio of the expected life years gained and the expected costs (see (2)): where $h(x,\omega)$ indicates the costs for sample lifehistory ω. The stochastic gradient ξ^s (see (12)) can be defined by:

$$R(x) = \frac{Eg(x,\omega)}{Eh(x,\omega)} \tag{13}$$

where $\gamma^s = \alpha^s/\beta^s$, and α^s, β^s are certain averaged values of $\bar{g}(x^k,\omega^k)$, $\bar{h}(x^k,\omega^k)$, $k=0,1,...,s$, and $\bar{h}_x(x^s,\omega^s)$ is the gradient of the sample cost function $\bar{h}(x^s,\omega^s)$ for policy x^s and lifehistory ω^s.

This paper addresses some issues which result from the special structure of the objective functions $G(x)$ and $H(x)$ in calculating ξ^s. Three different methods are used in removing the discontinuities which are first presented for the case of a single screening, and then for the general strategy with n screening invitations.

4. ONE SCREENING EXAMINATION

Conditional expectations.

The discontinuities in formula (1) that are related to the effects of screening tests (GROUP 3) can be removed by using expectations for the dichotomous variables (test result, participation, and cure) for a given disease history (T_L, T_P, T_I). For the sake of simplicity we use the same notation $\bar{g}(x,\omega)$ for new performance functions after taking some conditional expectations.

$$\bar{g}(x,\omega) = L(\omega).a(x).\begin{cases} s_{PI} & \text{if } T_P<x\le T_I \\ s_{ID}(x,\omega).c_{ID}(x,\omega) & \text{if } T_I<x\le T_D \\ 0 & \text{elsewhere} \end{cases} \tag{15}$$

Comparison with equation (1) shows that the events of group 3 have been replaced by their conditional expected values: participation rate $a(x)$, test sensitivity s_{PI} or $s_{IC}(x,\omega)$ in stages PI and IC respectively, and probability of cure $c(x,\omega)$.

The first element $L(\omega)$ is the number of life years lost without screening. In the crude microsimulation approach, this number is determined by drawing random variates T_C and T_L like in equation (1). In this case, $L(\omega)$ is nonzero only when $T_C<T_L$:

$$L(\omega) = \begin{cases} T_L - T_C & \text{if } (T_C<T_L) \wedge (T_C<T_H) \\ 0 & \text{elsewhere} \end{cases} \tag{16}$$

This discontinuity can be removed also by using the conditional expectation of the number of life years lost, which (in most cases) depends only on T_D, the age at which the cancer is diagnosed:

$$\bar{L}(\omega) = (1-M_H(T_D)) \int_{y=0}^{T_m-T_D} y \int_{z_{DC}=0}^{T_m-T_D-y} m_L(T_D+z_{DC}+y).f_{DC}(z_{DC};T_D).dz_{DC}\,dy \tag{17}$$

The term $(1-M_H(T_D))$ expresses the probability of having a hysterectomy for other reasons than cervical cancer before age T_D, the probability density function $f_{DC}(z;T_D)$ denotes the probability to die from the cancer at z years after diagnosis at T_D, and $m_L(a)$ is the probability density function of dying from other causes at age a. We assume a maximum age T_m, i.e. $Pr\{T_L \le T_m\} = 1$ and $m_L(t)=0$ for $t>T_m$. As a result, $\bar{L}(\omega) = 0$ if $T_D>T_m$.

Appendix A gives details on the calculation of $\bar{L}(\omega)$ and its derivative.

Avoiding simulation of cases with zero expected gain

From equation (15) it can be seen that the test at age x will have no effect at all if $x < T_P$ or $x > T_D$. Discontinuities occur at $x=T_P$ and $x=T_D$. These discontinuities can be avoided by restricting sampling to $T_P < x$ and $T_D > x$ The probability that x is in the range $[T_P,T_D]$ can be stated in two ways. First, it can be given in terms of the distributions that govern the disease process:

$$Pr\{T_P \leq x, T_D > x\} = \int_0^x (F_{PD}(T_m - t) - F_{PD}(x-t)).f_P(t)\,dt \tag{18}$$

where $F_{PD}(z)$ denotes the Pdf of the total duration ($=Z_{PI}+Z_{ID}$) of the screen-detectable stages, and f_P is the density function of F_P. Equation (18) can also be written in terms of the distribution of T_P and T_D, and is in the case of one screening equal to the prevalence of screen-detectable stages at age x:

$$B(x) = F_P(x) - F_D(x) \tag{19}$$

Now the "elsewhere" statement in (15) can be removed by using only histories for which $T_P<x<T_D$ and inserting the conditional probability $B(x)$:

$$g(x,\omega) = \bar{L}(\omega).a(x).B(x).\begin{cases} s_{PI} & \text{if } T_P<x\leq T_I \\ s_{ID}(x,\omega).c_{ID}(x,\omega) & \text{if } T_I<x\leq T_D \end{cases} \tag{20}$$

This equation shows that the expected number of life years gained is the product of five components: the prevalence of screen-detectable cases, the (age-dependent) participation $a(x)$, the (stage-dependent) effects of sensitivity and of cure, and the expected number of life years lost from the cancer $\bar{L}(\omega) = 0$.

A problem with (19) is the calculation of $F_D(x)$, which is not simple in a more general case with n screenings, or with many detectable stages. In the simplified model with two screen-detectable stages and with fixed duration z_{ID} of the second stage, a two-step procedure can be used. First T_P is simulated conditional on $T_P<x$, next, if $T_P+z_{ID}<x$, the probability that Z_{PI} is sufficiently large is used:

$$B(x;\omega) = \begin{cases} F_P(x).\left(F_{PI}(t_m - T_P - z_{ID}) - F_{PI}(x - T_P - z_{ID})\right) & \text{if } T_P+z_{ID}<x, \\ F_P(x) & \text{elsewhere} \end{cases} \tag{21}$$

The remaining discontinuity in (20) occurs at $x=T_I$, where the probability of detection and cure changes from s_{PI} to $s_{ID}(x,\omega).c_{ID}(x,\omega)$. Such a discontinuity is biologically not very plausible, and therefore the assumptions is made that the product $sc()$ of sensitivity and probability of cure decreases linearly in the screen-detectable invasive stage:

$$sc(x;\omega) = s_{ID}(x,\omega)c_{ID}(x,\omega) = \begin{cases} s_{PI} & \text{if } x \le T_I \\ s_{PI} \cdot \dfrac{T_D - x}{T_D - T_I} & \text{if } x > T_I \end{cases} \tag{22}$$

This leads to the general equation for the performance function in case of one screening at age x:

$$g(x;\omega) = a(x) \; . \; sc(x,\omega) \; . \; \overline{L}(T_D) \; . \; F_P(x) \; . \; \left(F_{PI}(T_m - T_P - z_{ID}) - F_{PI}(x - T_P - z_{ID})\right) \tag{23}$$

$$F_{PI}(y) = 0 \qquad \text{if } y \le 0 \tag{24}$$

The denominator $h(x,\omega)$ of the cost-effectiveness performance function which has been introduced in equation (2) expresses the expected proportion of the start population that have a screening test at age x, and it has three components that represent the status of three subpopulations at age x: $(h^N(x,\omega))$ persons that are (still) in state normal, $(h^P(x,\omega))$ persons that are in a state that can be detected by screening, $(h^D(x,\omega))$ persons in which cancer has already been diagnosed and treated. Only the first two groups will be invited for screening. For $h^N()$ we do not need a sample life history, since it is easy to use the exact proportion, which reflects the probabilities of being alive, of attending, and of not yet having entered preclinical disease states:

$$h^N(x,\omega) = a(x).(1 - M(x)).(1 - M_H(x)).(1 - F_P(x)) \tag{25}$$

For the second subpopulation we use our sample history ω to determine the proportion of women that are still detectable among all women who have entered the preinvasive state before age x:

$$h^P(x,\omega) = \left(1 - M_H(x)\right).\left(1 - M(x)\right).a(x).F_P(x).\left(1 - F_{PI}(x - T_P - z_{ID})\right) \tag{26}$$

The sum of the two components gives the expected proportion screened:

$$h(x,\omega) = \left(1 - M_H(x)\right).\left(1 - M(x)\right).a(x).\left(1 - F_P(x).F_{PI}(x - T_P - z_{ID})\right) \tag{27}$$

The gradient of the performance functions.

In the SQG optimization algorithm, the value of the sample performance function as given in (23) is only used in estimating the performance of the optimal strategy. More important is the **gradient** $\overline{g}_x(x^s, \omega_s)$ of the sample performance function, which is used to adjust the strategy x^s at each step s of the optimization. A crucial peculiarity of equation (23) is that the $\overline{L}(T_D)$ component implicitly depends on x, since $T_D = T_P + Z_{PI} + z_{ID}$ and both T_P and Z_{PI} are generated conditional on $T_P < x < T_D$.

Let us assume that T_P is defined by the random number ω_P, uniformly distributed on [0,1]:

$$T_P = F_P^{-1}(\omega_P . F_P(x)) \tag{28}$$

Then the derivative with respect to x is:

$$\frac{dT_P}{dx} = \omega_P f_P(x) \frac{1}{f_P(T_P)} = \frac{F_P(T_P)}{F_P(x)} \cdot \frac{f_P(x)}{f_P(T_P)} \tag{29}$$

Similarly, Z_{PI} is derived from a random number ω_I, uniformly distributed on [0,1]:

$$Z_{PI} = F_{PI}^{-1}\left((1-\omega_{PI}).F_{PI}(x-T_P-z_{ID}) + \omega_{PI}.F_{PI}(t_m-T_P-z_{ID})\right) \tag{30}$$

Note that $F_{PI}(x-T_P-z_{ID})=0$ if $T_P+z_{ID} \geq x$.

Equation (30) is the first example of calculating the derivative of a random variate Y with a minimum M_f and a maximum M_c, from a distribution F_Y. This situation frequently occurs in the case of more than one screening test. The general equations for the derivatives with respect to M_c and M_f are:

$$\frac{dY}{dM_c} = \frac{f_Y(M_c)}{f_Y(Y)} \frac{F_Y(Y)-F_Y(M_f)}{F_Y(M_c)-F_Y(M_f)} \tag{31}$$

$$\frac{dY}{dM_f} = \frac{f_Y(M_f)}{f_Y(Y)} \frac{F_Y(M_c)-F_Y(Y)}{F_Y(M_c)-F_Y(M_f)} \tag{32}$$

These equations can be used to derive the derivative of Z_{PI} with respect to x, by noting that Z_{PI} has minimum $M_f=x-T_P-z_{ID}$ and maximum $M_c=t_m-T_P-z_{ID}$:

$$\frac{dZ_{PI}}{dx} = \frac{-\left[F_{PI}(Z_{PI})-F_{PI}(M_f)\right] f_{PI}(M_c) \frac{dT_P}{dx} + \left[F_{PI}(M_c)-F_{PI}(Z_{PI})\right] f_{PI}(M_f) \left(1-\frac{dT_P}{dx}\right)}{\left[F_{PI}(M_c)-F_{PI}(M_f)\right] f_{PI}(Z_{PI})} \tag{33}$$

The derivative of $T_D=T_P+Z_{PI}+z_{ID}$ can now be obtained by combining (29) and (33), since z_{ID} does not depend on x. These equations can be used for the derivatives of $L(T_D)$ and ($F_{PI}(t_m-T_P-z_{ID})$ - $F_{PI}(x-T_P-z_{ID})$) with respect to x.

Finally, the gradient of the sample performance function (see (24),(23)) can be calculated:

$$\begin{aligned} \overline{g_x}(x;\omega) &= \overline{g}(x;\omega) \times \\ &\times \left[\frac{a_x(x)}{a(x)} + \frac{sc_x(x,\omega)}{sc(x,\omega)} + \frac{L_{T_D}(T_D,\omega)}{L(T_D,\omega)} \cdot \left(\frac{dT_P}{dx} + \frac{dZ_{PI}}{dx}\right) + \frac{f_P(x)}{F_P(x)} + \right. \\ &\left. + \frac{-f_{PI}(t_m-T_P-z_{ID}).\frac{dT_P}{dx} - f_{PI}(x-T_P-z_{ID}).\left(1-\frac{dT_P}{dx}\right)}{F_{PI}(t_m-T_P-z_{ID}) - F_{PI}(x-T_P-z_{ID})} \right] \end{aligned} \tag{34}$$

where:

$a(x)$, $a_{x_1}(x_1)$: are derived directly from data regarding participation to screening.

$sc(x;\omega)$ is defined in (22), with derivative:

$$sc_x(x;\omega) = \begin{cases} 0 & if \quad x \le T_I \\ \frac{s_{PI}}{z_{ID}} \cdot \left(\frac{dT_P}{dx} + \frac{dZ_{PI}}{dx} - 1\right) & if \quad x > T_I \end{cases} \tag{35}$$

$L(T_D, L(T_D,\omega))$ and $\overline{L_{T_D}}(T_D,\omega)$, are quantified on basis of observed cancer survival and life table data, see Appendix A.

Derivatives of T_P and Z_{PI} are given in (29) and (33).

The sample cost function $h(x,\omega)$ (the expected probability of a person having a screening examination) has gradient:

$$h_x(x;\omega) = h(x,\omega) \cdot \left[\frac{a_x(x)}{a(x)} + \frac{-m(x)}{1-M(x)} + \frac{-m_H(x)}{1-M_H(x)} + \right.$$
$$\left. + \frac{-f_P(x).F_{PI}(x-T_P-z_{ID}) - F_P(x).f_{PI}(x-T_P-z_{ID}).\left(1-\frac{dT_P}{dx}\right)}{1 - F_P(x).F_{PI}(x-T_P-z_{ID})} \right] \tag{36}$$

5. MULTIPLE SCREENINGS

In the general case screening takes place at ages $x = x_1,\ldots,x_n$. In generating life histories and calculating the performance function $\overline{g}(x,\omega)$ the same procedure that is used for 1 screening can be applied with some modifications and extensions. Calculation of the gradient $\overline{g}_x(x,\omega)$, however, requires additional analysis and is far more complicated. We will derive a recursive formula for calculating its values.

The performance function.

One component of the performance function, the expected number of life years lost at the age T_D of clinical diagnosis (equation (17)), is not changed. The sampling procedure for T_P and Z_{PI} is modified without many complications. The part which becomes much more complicated is the combined impact of participation, sensitivity, and cure rate, at successive screening examinations.

The extension of the techniques for avoiding cases with zero gain to the situation with more than one screening should do more than only exclude cases outside the screening age-range $[x_1,x_n]$. It should also exclude cases that cannot be detected by screening because their full preclinical period lies in the interval

between two consecutive tests. For a disease history the probability of being detectable on at least one screening is:

$$B^{(n)}(x) = Pr\{T_P \le x_1, T_D > x_1\} + Pr\{x_1 \le T_P \le x_2, T_D > x_2\} + \ldots = \\ = F_P(x_n) - F_D(x_1) - \sum_{i=1}^{n-1} \int_{x_i}^{x_{i+1}} F_{PD}(x_{i+1} - x) f_P(x)\, dx \qquad (37)$$

This equation cannot be used directly in a general case. Therefore, similar to the situation with one screening, an iterative procedure is used in which the conditional probability for being detectable is only being calculated after generating the age T_P at which the screen-detectable stage starts.

The procedure proceeds as follows: first generate T_P subject to $T_P<x_n$, and suppose that T_P occurs in screening interval i: $x_{i-1}<T_P<x_i$, $i=1,..,n$ and $x_0=x_{min}$ (see section 2). Now the history should be detectable at least at the first screening encountered, which means that $x_i<T_D \le t_m$, and we have an equation which is similar to (21) for the one-screening situation:

$$B(x;\omega) = F_P(x_n).(F_{PI}(t_m - T_P - z_{ID}) - F_{PI}(x_i - T_P - Z_{ID})) \qquad (38)$$

Note that $F_{PI}(x_i - T_P - z_{ID}) = 0$ in cases where $T_P + z_{ID} > x_i$.

The performance function for a history which becomes first screen-detectable at the i-th screening, and which remains screen-detectable until the k-th screening (i.e. $x_k<T_D<x_{k+1}$, $k=i,...,n.$, $x_{n+1} \equiv t_m$) is:

$$g^{i,k}(x;\omega) = \bar{L}(T_D) \cdot F_P(x_n) \cdot (F_{PI}(t_m - T_P - z_{ID}) - F_{PI}(x_i - T_P - z_{ID})) \cdot \sum_{j=i}^{k} u(x_j,\omega).sc(x_j,\omega) \qquad (39)$$

In this equation, the combined impact of participation, test-sensitivity, and cure-rate is included in the summation:

$$\sum_{j=i}^{k} u(x_j,\omega).sc(x_j,\omega) \qquad (40)$$

which represents the probability that the given history is detected and cured. The first component, $u_j(x_j, \omega)$, is the probability of being invited and attending at screening j, for which a set of recursive equations will be given. The second component has been defined in equation (22).
Participation patterns are modelled as a simple Markov chain: attenders to screening j-1 have probability $aa(x_j)$ to participate at the next screening, for non-attenders the probability is $an(x_j)$. Both probabilities are age-dependent, the average probability is equal to $a(x_j)$ which was already used for the case of a single screening test.
There is no need to make a distinction between attenders and non-attenders at previous screens when considering participation in the first screening at which a history can be detected (at age x_i). Hence, the overall participation probability can be used:

$$u(x_i,\omega) = a(x_i) \qquad (41)$$

At subsequent screenings at ages x_j, $j=i+1,..,k$, the participation pattern at earlier screens becomes important:

$$u(x_j,\omega) = w(x_{j-1},\omega).an(x_j) + v(x_{j-1},\omega).aa(x_j) \tag{42}$$

which involves $v(x_j,\omega)$ and $w(x_j,\omega)$. The multiplier $v(x_j,\omega)$ represents the probability of participation and having a non-positive result at round j, which in turn depends on the proportion false-negative results $sn(x_j,\omega)$:

$$v(x_j,\omega) = u(x_j,\omega) \; . \; sn(x_j,\omega)$$

$$sn(x_j,\omega) = \begin{cases} 1-s_{PI} & \text{if } T_P<x_j\leq T_I \\ (1-s_{PI})\dfrac{T_D-x_j}{z_{ID}} & \text{if } T_I<x_j\leq T_D \end{cases} \tag{43}$$

Note that $sn(.)+sc(.)=1.0$ only for pre-invasive cases, for invasive cases ($x_j>T_I$) there is a third possibility: detection without cure (see equation (22)).

The multiplier $w(x_j,\omega)$ is the probability of being invited and a non-participant; at the first round i in which the history is detectable w_i is simply:

$$w(x_i,\omega) = 1 - u(x_i,\omega) = 1 - a(x_i) \tag{44}$$

and at a subsequent round $j>i$:

$$w(x_j,\omega) = w(x_{j-1},\omega).(1 - an(x_j)) + v(x_{j-1},\omega).(1-aa(x_j)) \tag{45}$$

For $j>i$, the sum $u(x_j)+w(x_j)$ will in general be smaller than 1.0 because of the screen-detected cases at preceding smears.

The cost function.

The sample cost function $h^{i,k}(x,\omega)$ gives the expected number of screening tests per person, and is the sum of the expected number $h^{D,i,k}(x,\omega)$ for the sample life history and the exact expected number $h^N(x)$ for persons that will not enter the pre-invasive disease state before the age x_n of the last screening test:

$$h^N(x) = \left(1-F_P(x_n)\right).\sum_{j=1}^{n} a(x_j).\left(1-M(x_j).(1-M_H(x_j)\right) \tag{46}$$

$$h^{D,i,k}(x) = F_P(x_n)\times\left[\sum_{j=1}^{i-1} a(x_j).(1-M(x_j)).(1-M_H(x_j)) + \right. \\ \left. + (1-F_{PI}(x_i-T_P-z_{ID})).\sum_{j=i}^{k} u_j(x_j,\omega).(1-M(x_j)).(1-M_H(x_j))\right] \tag{47}$$

Gradient of the performance function for *n* screenings

We will use a similar approach for avoiding discontinuities as in the case of one screening. The condition used with multiple screenings is that the cancer remains screen-detectable at exactly the same tests when the screening ages $\boldsymbol{x} = x_1,..,x_n$ are slightly changed. This implies that the values of indices i (the first screening at which the disease can be detected) and k (the last screening at which the disease can be detected) do not change, which is achieved by adjusting the values of T_P and Z_{PI}, given the conditions:

$$\begin{aligned} x_{i-1} < T_P < x_i \\ x_k - T_P - z_{ID} < Z_{PI} < x_{k+1} - T_P - z_{ID} \end{aligned} \tag{48}$$

The derivatives of T_P with respect to x_{i-1} and x_i can now be obtained by applying equations (31) and (32), with $M_c = x_i$ and $M_f = x_{i-1}$.. The derivatives of T_P are equal to zero for all other screening ages x_j. In the special case when i=1 only the derivative with respect to x_i is relevant, which is then equal to the case of a single screening (equation (29)).
The derivative of Z_{PI} with respect to x_j is nonzero for $j = i-1, i, k, k+1$, and is again obtained by using equations (31) and (32), with $M_c = x_{k+1}-T_P-z_{ID}$ and $M_f = x_k-T_P-z_{ID}$.

In assembling the gradient of the performance function $\overline{g}(\boldsymbol{x},\omega)$ it is convenient to make a distinction between its three components: the disease history component $\overline{gd}(\boldsymbol{x},\omega)$, the clinical component $\overline{gc}(\boldsymbol{x},\omega)$, and the screening specific component $\overline{gs}(\boldsymbol{x},\omega)$:

$$\overline{g}^{i,k}(\boldsymbol{x};\omega) = \overline{gc}^{i,k}(\boldsymbol{x};\omega) \,.\, \overline{gd}^{i,k}(\boldsymbol{x},\omega) \,.\, \overline{gs}^{i,k}(\boldsymbol{x};\omega) \tag{49}$$

with:

$$\overline{gc}^{i,k}(\boldsymbol{x};\omega) = \overline{L}(T_D) \tag{50}$$

$$\overline{gd}^{i,k}(\boldsymbol{x};\omega) = (F_P(x_i)-F_P(x_{i-1})) \,.\, (F_{PI}(x_{k+1}-T_P-z_{ID})-F_{PI}(x_k-T_P-z_{ID})) \tag{51}$$

$$\overline{gs}^{i,k}(\boldsymbol{x};\omega) = \sum_{j=i}^{k} u(x_j,\omega).sc(x_j,\omega) \tag{52}$$

Apart from the derivatives of T_P and Z_{PI}, the contribution of the clinical component to the gradient is equal to the situation with a single screening. The contribution of the screening component is obtained by taking derivatives for the iterative set of equations (41)-(45) which is somewhat tedious but mainly a matter of good bookkeeping. Again, the modifications to the derivatives of T_P and Z_{PI} should also be taken into account.

The contribution of the disease history to the gradient is less straightforward, and depends on the derivative under consideration, and with a special situation if $i=k$. For example, when $i<k$ then the derivative with respect to x_i is:

$$\begin{aligned}\overline{gd}_{x_i}(x;\omega) = {} & f_P(x_i)\left(F_{PI}(x_{k+1}-T_P-z_{ID}) - F_{PI}(x_k-T_P-z_{ID}) \right) \\ & - \left(F_P(x_i) - F_P(x_{i-1}) \right)\left(f_{PI}(x_{k+1}-T_P-z_{ID}) - f_{PI}(x_k-T_P-z_{ID}) \right) \cdot \frac{d}{dx_i}T_P\end{aligned} \tag{53}$$

6. IMPLEMENTATION FOR THE CERVICAL CANCER MODEL

The cervical cancer model has been developed on basis of detailed screening data from British Columbia (van Oortmarssen & Habbema [1991]). Assumptions about the participation in screening, and about survival and mortality from cervical cancer and from other causes are adapted from the MISCAN cervical cancer model, see van Ballegooijen et al [1993].

Disease history

For Z_{PI} a Weibull distribution is assumed:

$$\begin{aligned}F_{PI}(z) &= 1-e^{-(\frac{z}{b})^c} \\ f_{PI}(z) &= c\,b^{-c}z^{c-1}(1-F_{PI}(z))\end{aligned} \tag{54}$$

The mean duration of Z_{PI} is 12 years, the shape c=1.7. The duration of the preclinical invasive stage is z_{ID}=4.0 years. A piecewise linear function is assumed for F_P:

$$F_P(t)=\begin{cases} p_0(t-t_0) & \text{if } t_0<t<t_1 \\ p_0(t_1-t_0)+p_1(t-t_1) & \text{if } t>t_1 \end{cases} \tag{55}$$

with derivative:

$$f_P(t)=\begin{cases} p_0 & \text{if } t_0<t<t_1 \\ p_1 & \text{if } t>t_1 \end{cases} \tag{56}$$

and parameter values (see van Oortmarssen & Habbema [1991]):

t_0= 18.0, t_1= 34.0,
p_0= 0.00211*0.16*0.74 = 0.00025,
p_1= 0.00106*0.60*0.74 = 0.00047.

Screening

The participation probability $a(x)$ is a function of age x, and is constant (75%) before age 50 and then decreases with 0.5% each year. The difference in participation probability between non-participants and participants at the preceding screening is $aa(x)$-$an(x)$ = 50%.
The detection and cure probabilities (equation (22)) have only one parameter s_{PI}=0.8.

Clinical course (see Appendix A)

The lethality is a function of age at diagnosis t_D and time since diagnosis y:

$$f_{DC}(x;t_D) = l(t_D).\lambda e^{-\lambda x} \tag{57}$$

The following function is used for age-dependent component (the long-term lethality $l(t_D)$), which is in agreement with Dutch survival data:

$$l(t) = \eta - \rho e^{-\mu(t-\tau)^2} \tag{58}$$

and has derivative:

$$l_t(t) = 2\mu\rho(t-\tau)e^{-\mu(t-\tau)^2} \tag{59}$$

The lethality is lowest at age τ=35 where it equals $\eta-\rho$=0.22, and never exceeds η=0.8. The steepness of the increase in lethality with age is governed by μ=0.002. The mean survival of women who die from the cancer is 2.5 years, i.e. λ=0.4.

The probability of death from other causes $M_L(a)$ is adapted from the Dutch life table:

a	$M_L(a)$	a	$M_L(a)$	a	$M_L(a)$	a	$M_L(a)$
0.0	0.0000	35.0	0.0167	60.0	0.0759	85.0	0.5604
15.0	0.0094	40.0	0.0205	65.0	0.1112	90.0	0.7656
20.0	0.0106	45.0	0.0264	70.0	0.1644	95.0	0.9199
25.0	0.0121	50.0	0.0365	75.0	0.2475	100.0	1.0000
30.0	0.0139	55.0	0.0519	80.0	0.3762		

Computational results

The model is implemented in a PC-based computer program. The SQG optimization was tested for the iterative sequence for screening age(s) x^s and estimated gain (life years) $\hat{G}^s$:

$$\begin{aligned} x^{s+1} &= x^s + 2.\frac{h}{h+s}.g_x(x^s,\omega^s) \\ \hat{G}^{s+1} &= (1-\gamma)\hat{G}^s + \gamma g(x^s,\omega^s) \\ h &= 10 \qquad \gamma = 0.00002 \end{aligned} \tag{60}$$

Results are presented in Figures 2-4. For one screening and 100,000 iterations, the optimal age is 49.0, and the expected number of life years gained per 100,000 women is 41.03. The optimal ages for 2 screenings are 43.4 and 54.8, with an expected gain of 65.6×10^{-5} life years. Note that adding a second screening will only give a

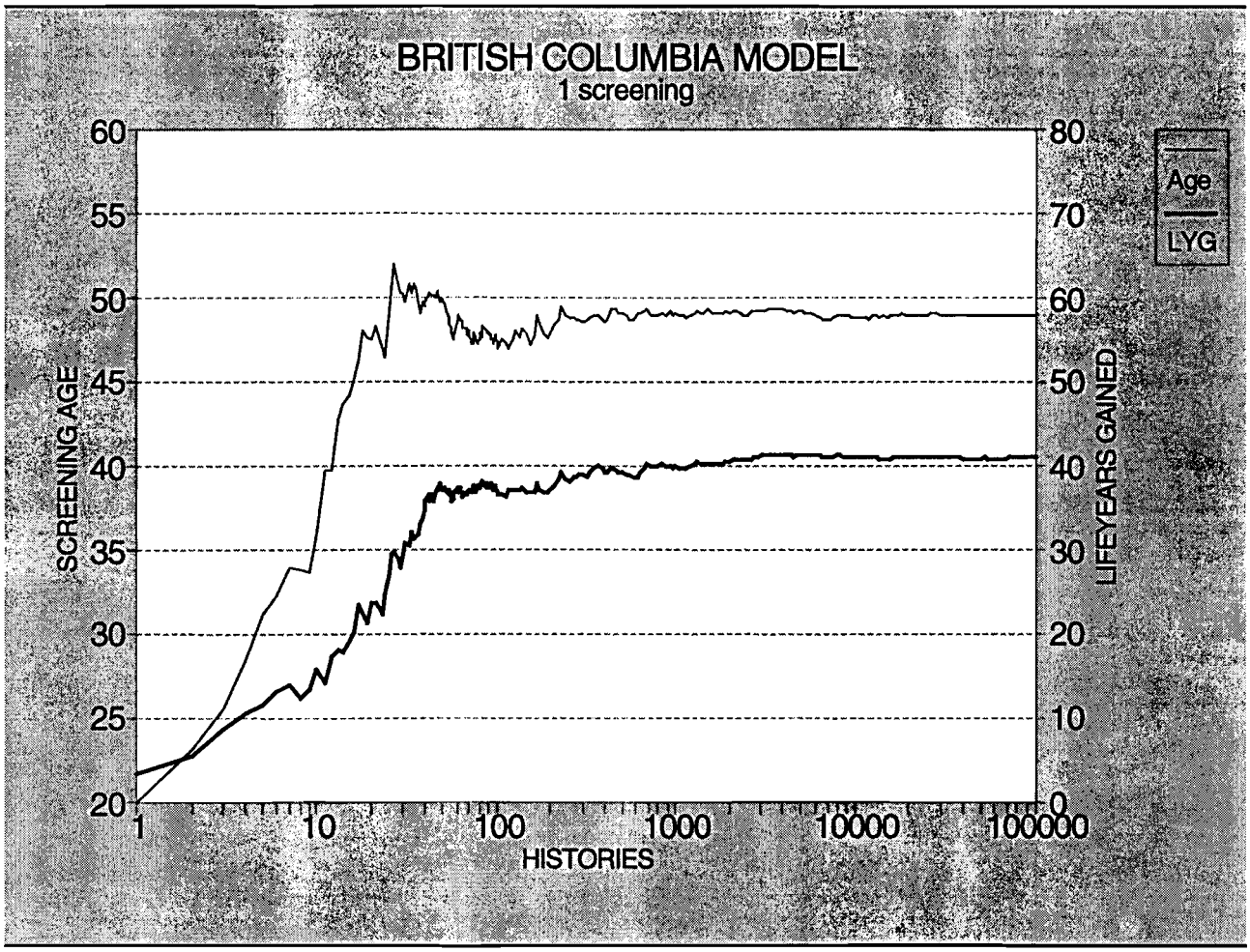

Figure 3 SQG optimization of cervical cancer screening policy, 1 screening test. Optimal screening age and expected Life Years Gained (LYG). Results of 100,000 iterations (histories) taking 2½ minutes on a 33Mhz 486DX PC.

60% increase in gain. The marginal gain will decrease further if more screenings are added. Repeated optimizations gave consistent results regarding optimal age(s) and gain, within a narrow range. For comparison, it can be mentioned that typical MISCAN runs involve a multitude of 100,000 histories, and will only give the estimated gain for one specified screening policy, whereas the SQG method yields the *optimal* policy with its expected gain.

Figure 5 shows optimization results for 1,2,3,...25 screening invitations, assuming equal intervals between invitations. For 3 and more invitations, finite-difference approximation (in a random direction) is used in stead of calculating the gradients analytically. The upper graph shows that the additional number of life-years gained decreases considerably for each additional invitation. With 25 invitations, only 4 times as many lifeyears are gained than with a single invitation, indicating that the marginal cost-effectiveness will deteriorate rapidly. All graphs show the mean and the 95% confidence interval for 10 optimization runs; for the lifeyears gained this interval is extremely small.

The middle graph shows the duration of the interval between successive invitations, and the bottom graph shows the corresponding ages of the first and last invitation. The curves for the first age and for the interval are not smooth. For example, when going from 5 to 6 invitations the first age drops from age 37 to 32. This is due to a peculiarity of the model: at age t_1=34 the onset level suddenly changes (from 2.5×10^{-4} to $4.7.10^{-4}$), and at 6 invitations the first age is forced to be below this age. A similar but smaller effect can be seen at 9 screening invitations, where the age of the second invitation crosses t_1.

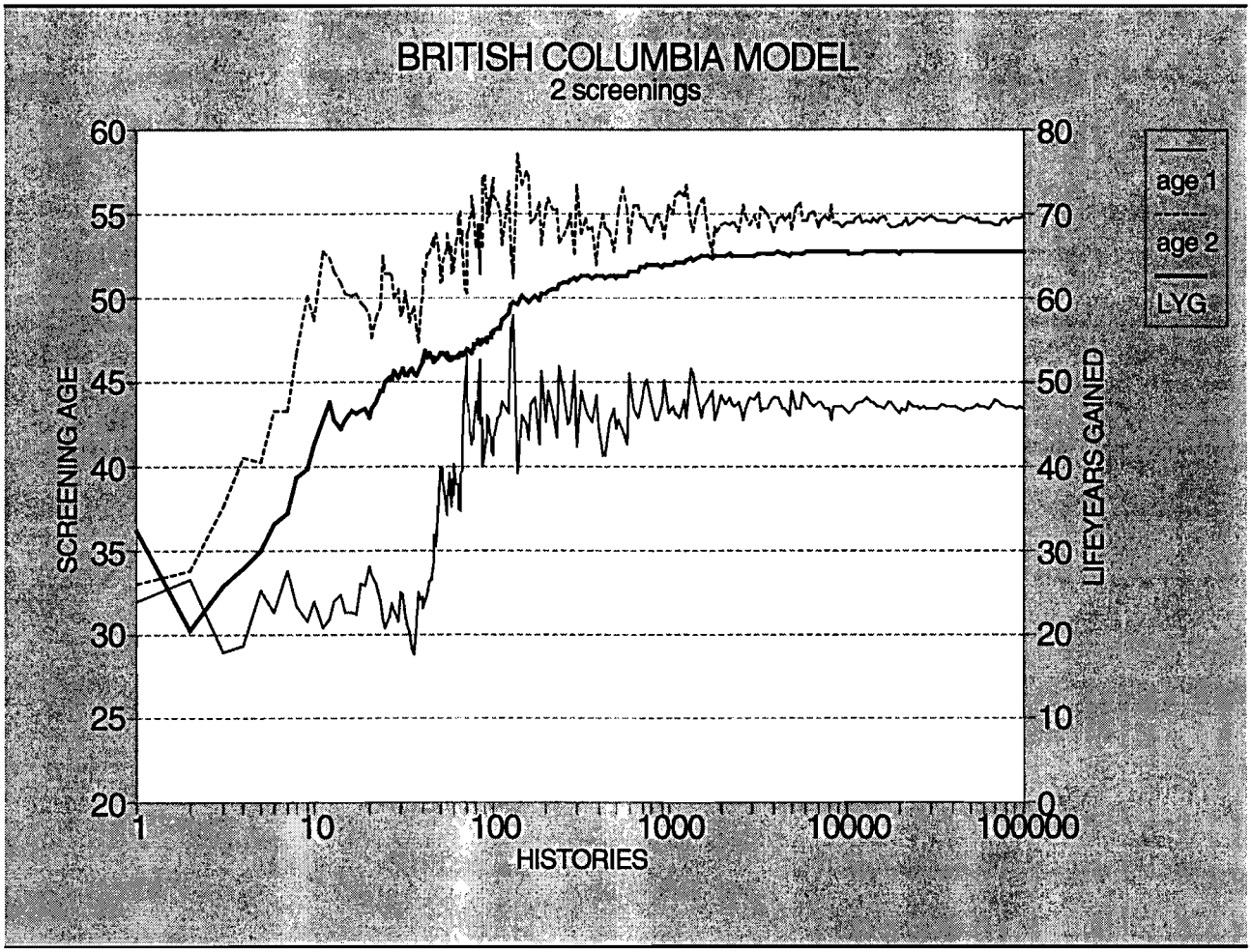

Figure 4 SQG optimization of 2 ages for cervical cancer screening, with associated Life Years Gained (LYG). 100,000 iterations (3 histories each) took 5½ minutes on a PC.

Only a very small (<1%) increase in life years gained was obtained when the intervals between invitations are allowed to change freely. For example, the optimal policy for 7 invitations and a fixed interval starts at age 31.7 and ends at age 65.5, interval 5.6 years; with free intervals the first and last ages are 29 and 65.5, and especially the first interval becomes longer: 10 years. However, the number of life years gained only increases from 120.0 to 121.1.

7. DISCUSSION

The SQG approach to optimization of stochastic systems has proven to be feasible for a model of cancer screening which contains most features of models that are being used in cost-effectiveness analyses of cancer screening, as an aid in decision making about screening strategies. This "simplified" model is already too complicated for conventional optimization techniques.

The implementation chosen in this paper is based on three types of refinements of the crude microsimulation as used in the MISCAN package. First, as much as possible, simulation of random events is replaced by taking expectations, conditional on the essential random events (the ages at which state-transitions in the disease process occur). Second, only life histories with non-zero expected gain are simulated. Third, in calculating gradients of the sample performance functions, the basic assumption is that a characteristics of the disease history are not changed by small perturbations of the decision variable (the screening ages), see L'Ecuyer [1991] for different approaches for perturbation-based methods. In the model considered, the history is

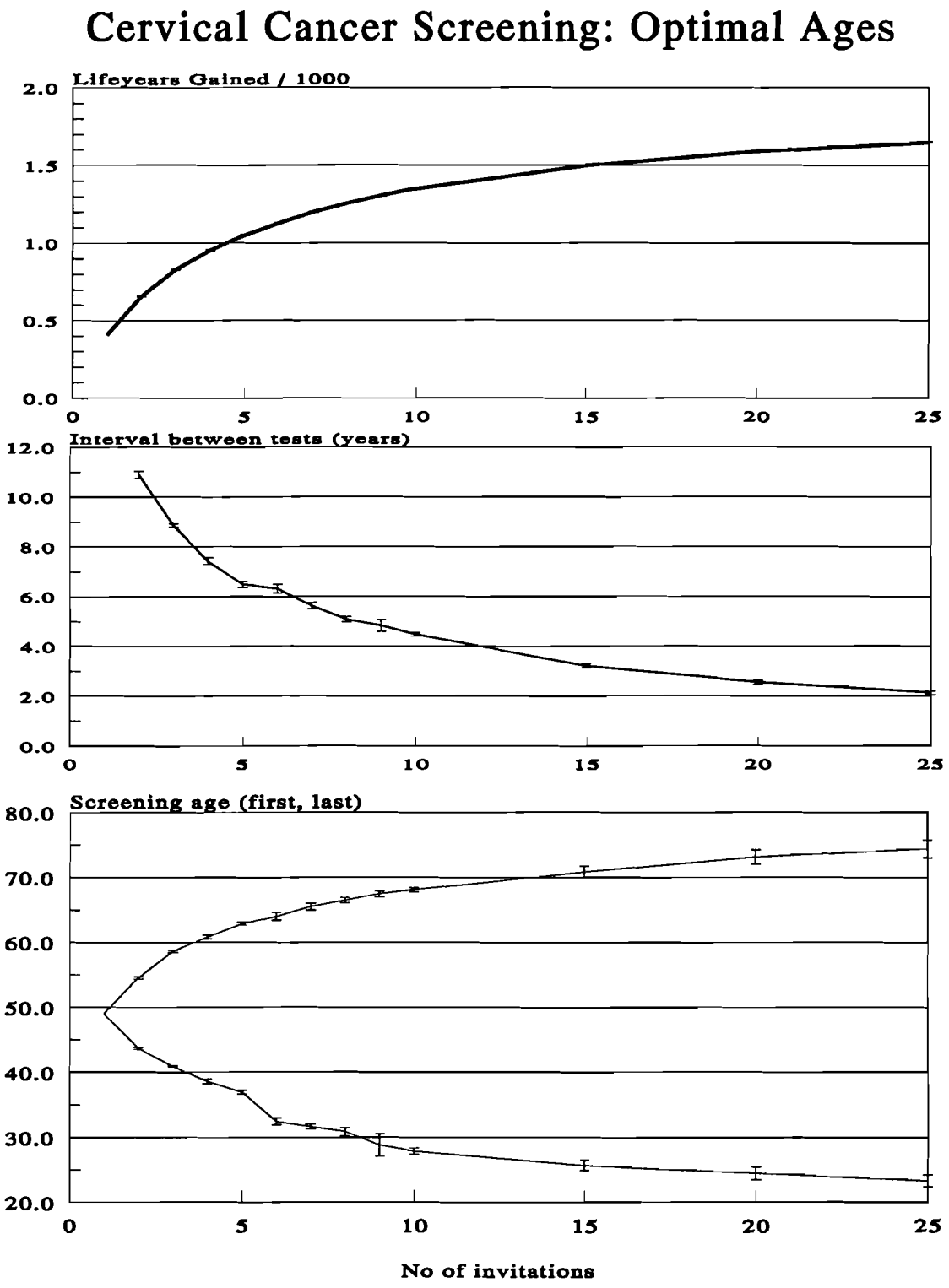

Figure 5 SQG optimization for different number of screening tests.

characterized by the screenings-interval in which transitions between disease states occur.
After making these refinements, it is possible to derive exact formulas for the stochastic gradient of a sample performance function (for a simulated life-history). This last analytical step is not mandatory, however. An alternative is to use finite-difference approximations (FDA) of the gradient, which require far less investment in the mathematics of the model. But FDA has the disadvantage of each approximation method: the possibility of bias. In fact, the FDA alternative has been used in debugging the model, which showed a practical disadvantage of the analytical calculation of the gradient: the risk of errors in the analysis.

In refining the simulation procedure, one departure from the existing MISCAN disease models has been made. Both sensitivity and cure rate, which are constant within disease states in MISCAN, are assumed to change continuously within states in order to avoid discontinuities at state boundaries. Strictly speaking, this departure is not necessary, since smoothing methods exist to deal with discontinuities (see Ermoliev,Norkin and Wets [1994]). But it is far more convenient to remove avoidable discontinuities like these ones occurring in MISCAN, that have no biological justification.

The work presented in this paper can be extended along a number of lines.
A generalization to a more general model would include a more detailed disease process, with multiple stages and different possible trajectories through stages, including the possibility of regression. Also, transitions and dwelling times would in general be made age-, time- and cohort-dependent.
In recent years, a large body of evidence has been obtained supporting the hypothesis that cervical cancer may (in part) be caused by certain strains of Human Papilloma Virus (HPV) which are transmitted sexually. Screening tests for detection of HPV have been developed, and now the evaluation of screening policies has become more complicated because the HPV test may replace the existing (cytologic) test, or the two tests can be combined. The present model could be extended by adding a second disease (HPV) consisting of one stage, and which gives a high risk of developing a cervical cancer process, starting in the preclinical invasive (PI) stage.

One important extension regarding cost-effectiveness performance function (which is based on the ratio of the number of life years to the number of screenings) is to use the SQG approach for generating the efficient frontier of all Pareto-optimal screening strategies (see Koopmanschap *et al.*[1990]). The performance function can be refined further by using quality-adjusted life years. Other performance functions might also be considered, e.g., the reduction in mortality or in incidence of (advanced) disease. On the cost side, the extra costs and savings for medical treatment, and non-medical costs, could be taken into account.
A further generalisation is to embed the model in a real population, since in practice decisions about screening have to be made for populations instead of for cohorts. This also means that discounting of cost and effects has to be possible, and, in the case of cervical cancer screening, that the history of screening up to the timepoint at which a policy decision has to be made should be included in the model.

Apart from these refinement of the model and the performance function, two other areas deserve further attention. Supplementary work needs to be done regarding the choice of step size, projection operator, and other parameters of the SQG algorithm (equation (12)), using existing experience in this field, see for example Gaivoronski[1988]. And an important extension of the methodology would be to evaluate the impact of uncertainty about the model and its parameters, such as the mean duration of screen-detectable stages, test sensitivity, cure probability, participation rate to screening, etc.

A completely new area of application of this approach is in infectious diseases for which stochastic simulation models have been developed (ONCHOSIM, see Plaisier[1990]) or are under construction. The main complication is that individual histories are influenced (e.g., by infection) by other individuals. This leads to stochastic models with strongly interacting processes, and non-linear feedbacks.

APPENDIX:Expected Life years lost from cancer at given age of diagnosis

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Appendix A

CALCULATING THE LIFEYEARS LOST FROM CANCER

In this appendix formulas are presented which can be used to calculate, *at the moment of diagnosis* t_D, the expected lifeyears lost because of death from cervical cancer, and its derivative with respect to t_D . These formulas can be used instead of the full microsimulation procedure in which, when the disease history has reached the time of clinical diagnosis T_D, random numbers are generated for the survival time Z_{DC}, the age at death from other causes T_L, and the age T_L at which a hysterectomy is carried out for other reasons than cervical cancer. Then, the number of lifeyears lost for this sample is:

$$L_{LY}(T_D) = \begin{cases} T_L - (Z_{DC} + T_D) & \text{if} \quad (T_L > Z_{DC} + T_D) \wedge (T_H > T_D) \\ 0 & \text{elsewhere} \end{cases} \qquad (1)$$

The main advantages of using the expected value are:

- reduction of variance in the simulation;
- the derivative of the expected value with respect to t_D can be used for calculation of the gradient of the objective function with respect to characteristics of a screening policy.

Quite general assumptions are made about the lifetable and the survival distribution.
The situation considered is the baseline case in which no screening is applied, and in which cancers are diagnosed on basis of symptoms and complaints. The main simplification made is that only one clinical stage is considered, extension to a situation with several clinical stages (according to the stage classification at time of the primary treatment) is not very difficult, however.

If a woman is diagnosed as having cervical cancer at age t_D, the expected number of lifeyears lost from dying of this cancer is given by:

$$L(t_d) = \left(1 - M_H(t_d)\right) \int_{y=0}^{\infty} y \int_{x=0}^{\infty} m_L(t_d + x + y) . f_{DC}(x; t_d) . dx \; dy \qquad (2)$$

The probability to die from other causes at an age T_L before age a is represented by $M_L(a) = Pr\{T_L \leq a\}$, with probability density $m_L(a)$. The probability to have a hysterectomy for other reasons than cervical cancer at age T_H before age a is represented by $M_H(a) = Pr\{T_H \leq a\}$, with probability density $m_L(a)$. The other component $f_{DC}(x; t_D)$ represents the probability density of dying from cervical cancer at x years following the treatment at age t_D, with corresponding distribution function $F_{DC}(x; t_D) = Pr\{T_C \leq t_D + x; T_D = t_D\}$. The two causes of death (cervical cancer and other causes, respectively) are assumed to be independent.

A reasonable representation of survival data can be obtained in most cases by assuming that only a certain age-dependent fraction $l(t_D)$ of cases treated at age t_D are destined to die from

the cancer, and that the survival time for these lethal cases follows an exponential distribution with rate λ:

$$f_{DC}(x;t_D) = l(t_D).\lambda e^{-\lambda x} \tag{3}$$

Equation (2) can be written as:

$$L(t_d) = \left(1 - M_H(t_d)\right) \int_{x=0}^{\infty} E_{LY}(t_d+x).f_{DC}(x;t_d)\,dx \tag{4}$$

where $E_{LY}()$ represents the expected number of lifeyears after a certain age y:

$$E_{LY}(y) = \int_{x=0}^{\infty} x.m_L(y+x)\,dx \tag{5}$$

Note that the (conditional) remaining life-expectancy for persons who are alive at age y should be obtained by dividing (5) by $(1-M_L(y))$. In agreement with demographic practice, it is assumed that $M_L(y)$ is a piecewise linear function:

$$\begin{aligned} &M_L(y) = p_i - r_i.(z_i - y) \qquad z_{i-1} < y \le z_i,\ i=2,..,n_L \\ &r_i = \frac{p_i - p_{i-1}}{z_i - z_{i-1}}, \quad p_1 = 0.0, \quad p_{n_L} = 1.0 \end{aligned} \tag{6}$$

Using this functional form, (5) can be written as follows, for age y in $[z_{k-1}, z_k]$:

$$E_{LY}(y) = (z_k - y).(1 - p_k + r_k \frac{z_k - y}{2}) + \sum_{i=k+1}^{n_L} (z_i - z_{i-1}).(1 - \frac{p_i + p_{i-1}}{2}) \tag{7}$$

or, equivalently:

$$E_{LY}(y) = S_k + (1 - p_k).(z_k - y) + \frac{r_k}{2}.(z_k - y)^2 \tag{8}$$

where:

$$S_k = \sum_{i=k+1}^{n_L} (z_i - z_{i-1}).(1 - \frac{p_i + p_{i-1}}{2}) \tag{9}$$

or, by iteration:

$$S_k = S_{k+1} + (z_{k+1} - z_k).\left(1 - \frac{p_{k+1}+p_k}{2}\right) \qquad 0 \le k < n_L \qquad (10)$$
$$S_{n_L} = 0$$

The expected number of lifeyears lost for a women who is treated for cervical cancer at age t can be calculated from (4) and (8):

$$L(t) = l(t).(1 - M_H(t))$$
$$\int_0^{\infty} \lambda.e^{-\lambda x}.\left[S_{k_{t+x}} + (1 - p_{k_{t+x}}).(z_{k_{t+x}} - t - x) + \frac{r_{k_{t+x}}}{2}.(z_{k_{t+x}} - t - x)^2 \right] dx \qquad (11)$$

Note that $l(t)$, the (long-term) letality risk of cases diagnosed at age t, is simply a multiplication factor.
By defining k_t as the agegroup of the lifetable in which the cancer is diagnosed at time t, i.e. k_t: $z_{k_t-1} < t \le z_{k_t}$, (11) can be rewritten by introducing a distinction between lifeyears $L_{k_t}(t)$ lost in the (lifetable) age-interval k_t, and lifeyears L_k^{λ} lost in each of the subsequent intervals:

$$L(t) = l(t) \;.\; (1 - M_H(t)) \;.\; [L_{k_t}(t) + e^{\lambda t}.\sum_{k=k_t}^{n_L} L_k^{\lambda}] \qquad (12)$$

The first component is a rather complicated function of the age at diagnosis t:

$$L_{k_t}(t) = a_{k_t}.(e^{-\lambda(z_{k_t} - t)} - 1) + b_{k_t}.(z_{k_t} - t) + c_{k_t}.(z_{k_t} - t)^2 \qquad (13)$$

where the constants a_k, b_k, and c_k are defined for each lifetable interval k:

$$a_k = -S_{k_t} + (1 - p_k)/\lambda - r_k/\lambda^2$$
$$b_k = 1 - p_k - r_k/\lambda \qquad (14)$$
$$c_k = r_k/2$$

The lifeyears lost in subsequent interval do not depend on t except for the multiplication factors $l(t)$ and $e^{\lambda t}$:

$$L_k^{\lambda} = a_k(e^{-\lambda z_k} - e^{-\lambda z_{k-1}}) + e^{-\lambda z_{k-1}}\left(c_k(z_{k-1}-z_k)^2 - b_k(z_{k-1}-z_k)\right) \tag{15}$$

Gradient

The derivative of the number of lifeyears lost can be obtained from (12):

$$\begin{aligned}\frac{d}{dt}L(t) &= l_t^H(t).L_{k_t}(t) + l(t).(1-M_H(t)).l_{k_t}(t) + \\ &+ [l_t^H(t).e^{\lambda t} + l(t).(1-M_H(t)).\lambda e^{\lambda t}].\sum_{k=k_t}^{n_L} L_k^{\lambda}\end{aligned} \tag{16}$$

where $l_t^H(t)$ denotes the derivative of $l(t).(1-M_H(t))$, and $l_{k_t}(t)$ is the derivative of $L_{k_t}(t)$:

$$l_{k_t}(t) = a_{k_t}\lambda e^{-\lambda(z_{k_t}-t)} - b_{k_t} - 2c_{k_t}(z_{k_t}-t) \tag{17}$$

The age-dependent lethality $l(t)$ and its derivative $l_t(t)$ are given in the main text.

Extensions

In many cancers, the hazard rate is not constant, but is higher in the first years and lower after 5-10 years since treatment. This can be incorporated by using a double (mixed?) exponential survival time distribution, and the formulas presented in this appendix can be adapted easily in this case.
A more complicated extension will be to incorporate the effect of discounting. This involves weighting of lifeyears gained: years in the near future have a higher weight than years gained later. This extension can start with the following formulas which take t_d as baseline point for discounting.
Equations (4) and (5) will then be modified:

$$L^{\delta}(t_d) = (1-M_H(t_d)) \cdot \int_{x=0}^{\infty} E_{LY}^{\delta}(t_d+x).e^{-\delta x}.f_{DC}(x;t_d)dx \tag{18}$$

$$E_{LY}^{\delta}(y) = \int_{x=0}^{\infty} \frac{1}{\delta}.(1-e^{-\delta x}).m_L(y+x)dx \tag{19}$$

with $\delta = \ln(1+d)$ and d is the annual discount rate.