Computer Methods and Programs in Biomedicine 20 (1984) 79–93
Elsevier

CPB 00674

The MISCAN simulation program for the evaluation of screening for disease

J.D.F. Habbema, G.J. van Oortmarssen, J.Th.N. Lubbe and P.J. van der Maas

Department of Public Health and Social Medicine, Medical Faculty, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

The computer program MISCAN is developed for use in evaluation of mass screening for disease. The program uses Monte Carlo simulation. It produces output on the results of screening projects and on the effects of screening on morbidity and mortality on the individual and population level. The calculations are based on models of the natural history of the disease and of the impact of screening on the natural history. The approach is such that considerable flexibility exists in specifying the structure of the model and its parameters. The program consists of two parts. The DISEASE part can be used for simulating the epidemiology of the disease when no screening is taking place; it requires input on the population and on the disease process. The SCREENING part is to be used in combination with the DISEASE part. It is intended for simulation of the results and effects of a screening project. It requires input on the properties of the screening tests, the consequences of early detection by screening, and the policy (ages and intervals between screens) of the project.

MISCAN can be used for finding model assumptions regarding the disease process and the impact of screening that give a good explanation of the observed results of a screening project. Such an analysis proceeds in two steps. First, MISCAN is used to calculate simulated results of the project, based on specific assumptions. Next, these results are tested against the observed results, in order to assess the acceptability of the assumptions. MISCAN can also be used for optimization of the screening policy by simulating the cost and benefit components of a large number of different screening policies.

Monte Carlo simulation Mass screening Natural history Screening test Screening policy Cost–benefit analysis Microsimulation

1. Introduction

Evaluation of screening for the early detection of disease has two main concerns [1]. First, one would like to know what conclusions can be drawn from an analysis of the observed results of screening projects. These conclusions should concern aspects such as attendance to screening, costs of screening, characteristics of the screening test, the natural history of preclinical disease, and, ultimately, the effect of screening on mortality and morbidity.

Second, one would like to make recommendations about the choice of a future screening policy. A policy is roughly defined by the ages at which screening should take place, and the screening tests used at these screens. The policy that is judged to be optimal may be quite different from the policies adopted during the projects for which the results have been analysed.

Both the analysis and the optimization stage of evaluation involve inherently complex reasoning. In the analysis stage, the results of a screening project (e.g. yield at successive screening rounds, interval cases, and mortality before and after screening) are determined by the combined influence of a large number of aspects or factors and their complex interrelations. Among these factors

are the incidence and duration of preclinical disease, the attendance to screening, the quality of the screening test, and prognosis after preclinical detection.

In the optimization stage, the various costs, risks and benefits of screening should be calculated for many different alternative policies. These favourable and unfavourable consequences can be analysed further by cost effectiveness and cost–benefit analysis, in order to find the policy with the highest net benefit (which may be the policy 'do not screen at all').

The complexity of the screening evaluation problem has led to the development of mathematical models and application of computer simulation programs based on these evaluation models, in particular for cancer screening [2]. The more important models are included in [3–7]. The MISCAN computer program (MISCAN stands for MIcrosimulation SCreening ANalysis), to be described in this paper, is based on microsimulation or Monte Carlo simulation. This simulation technique has become a viable means for screening evaluation in view of the capacity of the computers that are currently available. Basically, the MISCAN program first simulates a large number of individual life histories, according to assumptions (input specifications) concerning the epidemiology and the natural history of the disease under consideration. Then, these life histories are subjected to screening, according to assumptions (input specifications) on screening policy, attendance, characteristics of the screening test, and prognostic consequences of early detection. Some of the life histories will be changed by this simulated screening experience. These changes, be it in a favourable or in an unfavourable sense, constitute the simulated effect of screening.

This article is intended as an introduction to the MISCAN program. The structure of MISCAN will be discussed in section 2. A more detailed description of some important aspects of the program is given in section 3 and in the appendix. Section 4 discusses the output for the two stages of evaluation: analysis and optimization. In section 5 some other model approaches are briefly introduced and compared to MISCAN.

2. The structure of MISCAN

The basic structure of MISCAN is illustrated in Fig. 1. It relates the program to its input and output, and to the way in which the output is used in screening evaluation.

The DISEASE part of the program refers to a population in which no screening takes place.

The SCREENING part of MISCAN applies to the population where screening for the disease under consideration takes place. As a consequence of this screening, the morbidity and mortality experience of the population will be modified. This two-part structure allows for the use of the DISEASE part as a program on its own, in case one is only interested in modelling the natural history of a disease.

The DISEASE part of the program generates a large number of life histories. Together, the life histories constitute the target population that will be screened in the SCREENING part. The stochastic model underlying the simulation of the population is specified by the input of the program. The input relates to the population (e.g. the life table), the epidemiology of the disease (e.g. age-specific incidence) and the disease process. Important aspects of the disease process include disease states into which preclinical and clinical disease is subdivided, the duration of preclinical disease, the probability that preclinical disease will regress spontaneously, etc. (see section 3 for more details). The output of the DISEASE part consists of the simulated life histories. All types of epidemiological data are computed from the aggregation of life histories: the incidence of clinical disease, the prevalence of the disease states, the mortality, and survival figures. These stimulated data can be printed in age-specific tables. It is also possible to store the figures in data files that are suited for further analysis. This is especially useful in the statistical testing for differences between simulated and observed figures.

The input of the SCREENING part consists of assumptions on the screening process (properties of the screening test, prognosis after early detection) and of a specification of the screening policy. A typical screening policy requires input of the age at which persons will be invited for the first time,

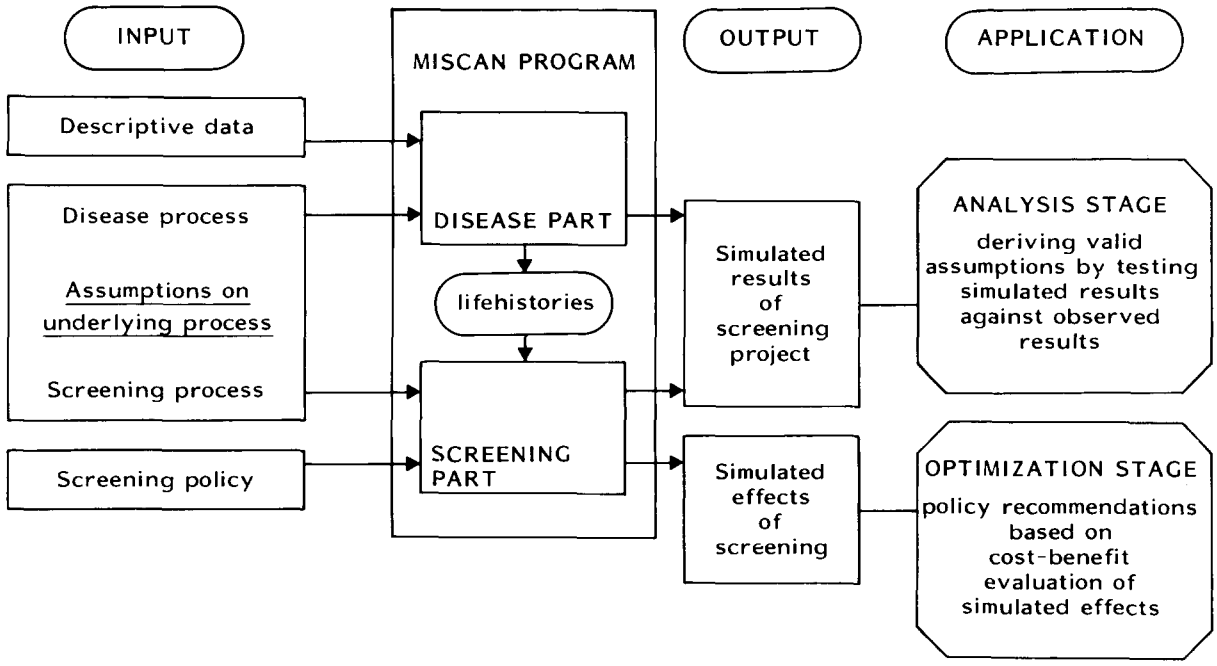

Fig. 1. Structure of the MISCAN simulation program for the evaluation of screening for disease.

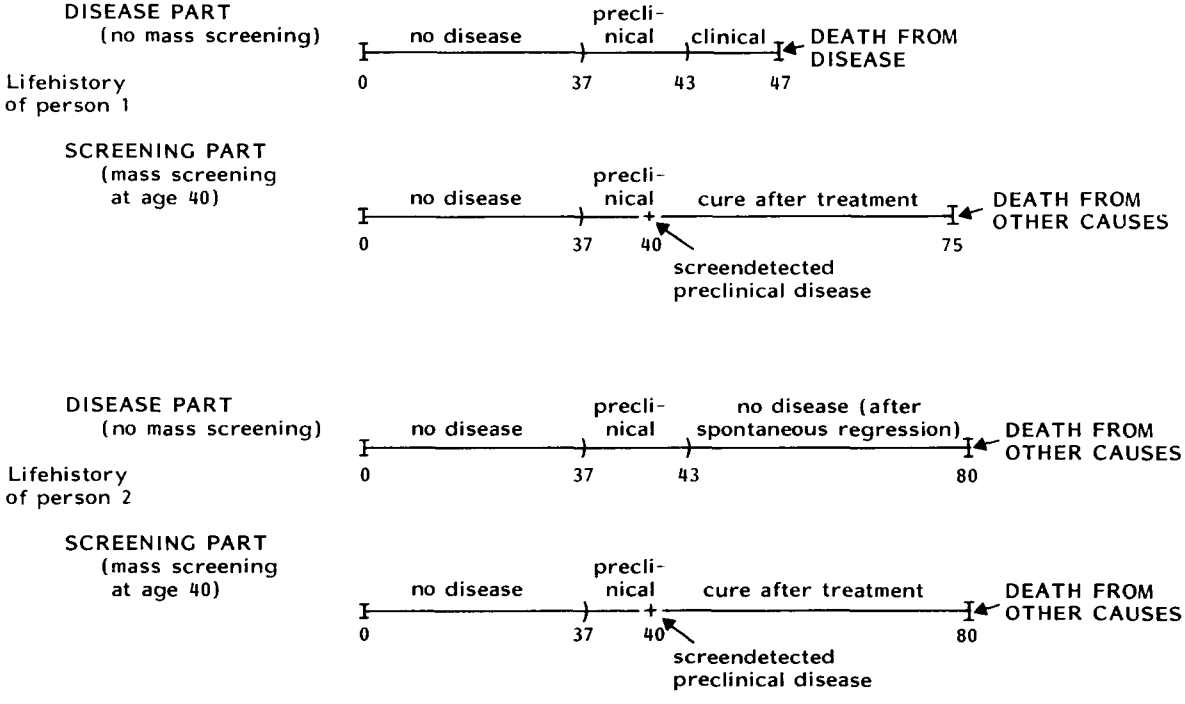

Fig. 2. Two examples of life histories generated by the MISCAN simulation program.

the time intervals between repeat screenings, the total number of screenings that is offered, and the attendance figures to initial and to repeat screenings. The results of screening are simulated for each person whose life history was generated in the DISEASE part. Changes in these life histories can occur as a consequence of a positive (either false or true) screening result. The output of the SCREENING part consists of the simulated screening results (e.g. the number of cases detected, number of cases missed, mortality among screen-detected cases) and of the simulated effects of screening (e.g. the number of lives/life years saved, and the number of unnecessarily treated persons). Again, the output can be stored in data files to enable further calculations with the simulated results and effects.

Fig. 2 gives two examples of screen-induced changes in life histories. For person 1, the change is favourable: without screening, the person dies from the disease at age 47; when screening is performed at age 40, the preclinical disease is detected and early treatment results in cure: 28 life years are gained.

For person 2, the effect is unfavourable. In the DISEASE part, preclinical disease starts at age 37, and the disease disappears after 6 years without being diagnosed. In the screening part, the disease is detected. This is an example of unnecessary treatment caused by screening. This treatment does not alter the life expectation of the person, but it does influence the quality of life and the health care expenditures.

3. Modelling a mass screening project with MISCAN

A study of the input items is an appropriate way for getting acquainted with the possibilities and limitations of MISCAN. The input of the program is shown in greater detail in Fig. 3, together with the sections where each of the input items will be described.

3.1. The population: preclinical incidence, life table, cohort differences, stratification, and prevention

Consider a population consisting of a single homogeneous birth cohort. In this case, the principal items of interest are the preclinical disease incidence and the life table. The disease incidence can be specified by giving the cumulative probability of acquiring the disease in its earliest screen-detectable state. The life table contains, for a series of ages, the probability of death from other causes than the target disease.

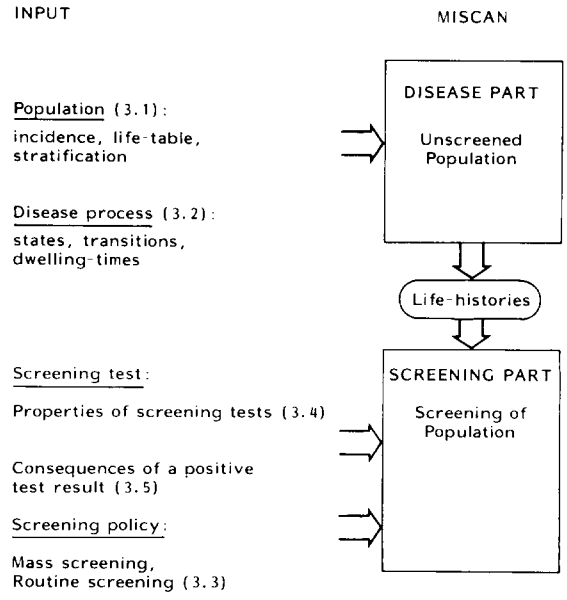

Fig. 3. Overview of the most important items for the MISCAN simulation program. (The sections in which the items are described are indicated between parentheses.)

In a more detailed specification, the population can be considered to consist of a number of different birth cohorts, and a (further) subdivision into different strata is also possible. In the DISEASE part, both a birth cohort and a stratum is defined by its relative size (proportion of the total population), and by its preclinical disease incidence. Moreover, the mortality experience as summarized in the life tables may differ between cohorts or strata. In the SCREENING part, strata may differ with respect to participation in a screening program. Birth cohorts may also differ with respect to the ages at which screening takes place; this option can be used in the case of a screening project that is starting in a given calendar year.

In some applications, the disease is sometimes prevented or interrupted by an intervention that is

applied for disease-unrelated reasons. For example, cervical cancer can be prevented or interrupted by an extirpation of the uterus because of complaints that have nothing to do with cervical cancer. Such an intervention removes the person from the population at risk. The probabilities of the intervention are defined in two steps: a cumulative probability (over all ages), and an age distribution. Both the cumulative probability and the age distribution can be varied between birth cohorts and between strata.

3.2. The disease process

3.2.1. Elements of the disease process

In the DISEASE part of MISCAN, disease histories are simulated in an unscreened population. A disease history is only simulated for those persons that enter the first screen-detectable state (see section 3.1).

The disease process is defined by the states in which the process has been subdivided, by the probabilities of transition between states, and by the dwelling times in the states. A disease history is represented by a sequence of disease states and the ages at which the person enters these states or, equivalently, the dwelling times in these states (see Fig. 2). It is assumed that each combination of a next state and the dwelling time in the present state essentially depends on the present state only; optionally it may also depend on the age at which the present state has been entered, and on the dwelling time in the preceding state. These options leave ample space for modelling interactions (for instance, it can be used for letting the growth rate of a tumour depend on the age of the person).

3.2.2. The states

First of all, all relevant disease states should be defined. These states should be classified into a number of groups, each with its own role during the simulation of the disease process and the screening process. The five most important groups of states are:

End ('absorbing') states States in which the simulation of a disease history ends. Two end-states have to be defined in any application:

* DEATH FROM DISEASE and DEATH FROM OTHER CAUSES.

Clinical states States in which the disease has been diagnosed. In the DISEASE part of MISCAN, only clinical (symptomatic) diagnosis occurs; in the SCREENING part, detection by screening will also be possible.

Screen-eligible states States in which persons are eligible for screening. In simulating a screening project, it may be relevant to exclude persons in specific states from screening, e.g. persons in a clinical state or people who are no longer at risk because of a disease-unrelated intervention.

Preclinical normal states States in which a positive result of a screening test is to be interpreted as false positive.

Preclinical disease states States in which a positive result of a screening test is to be interpreted as true positive.

Fig. 4 gives a diagrammatic representation of the different groups of states. Fig. 5 gives a (simple) model of cervical cancer. All preclinical disease states and state NORMAL are screen eligible: the true test result in state NORMAL is negative. In states CARCINOMA IN SITU and PRECLINICAL INVASIVE CANCER the true result is positive; in this case a transition to a screen-detected clinical state will follow.

3.2.3. Transitions between states

The standard method of defining transitions in the MISCAN program is by specifying the transition probabilities to possible subsequent states. Each transition has its corresponding probability

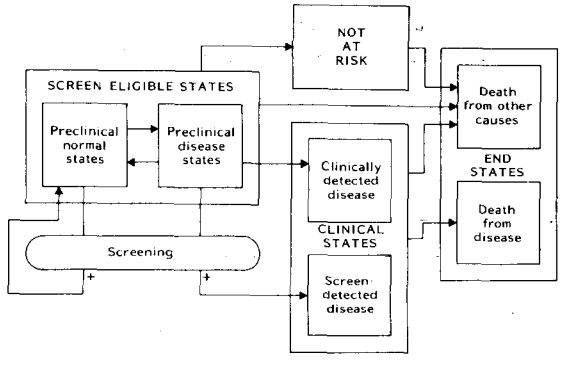

Fig. 4. The important groups of disease states in the MISCAN simulation program, and the usual transitions between these groups.

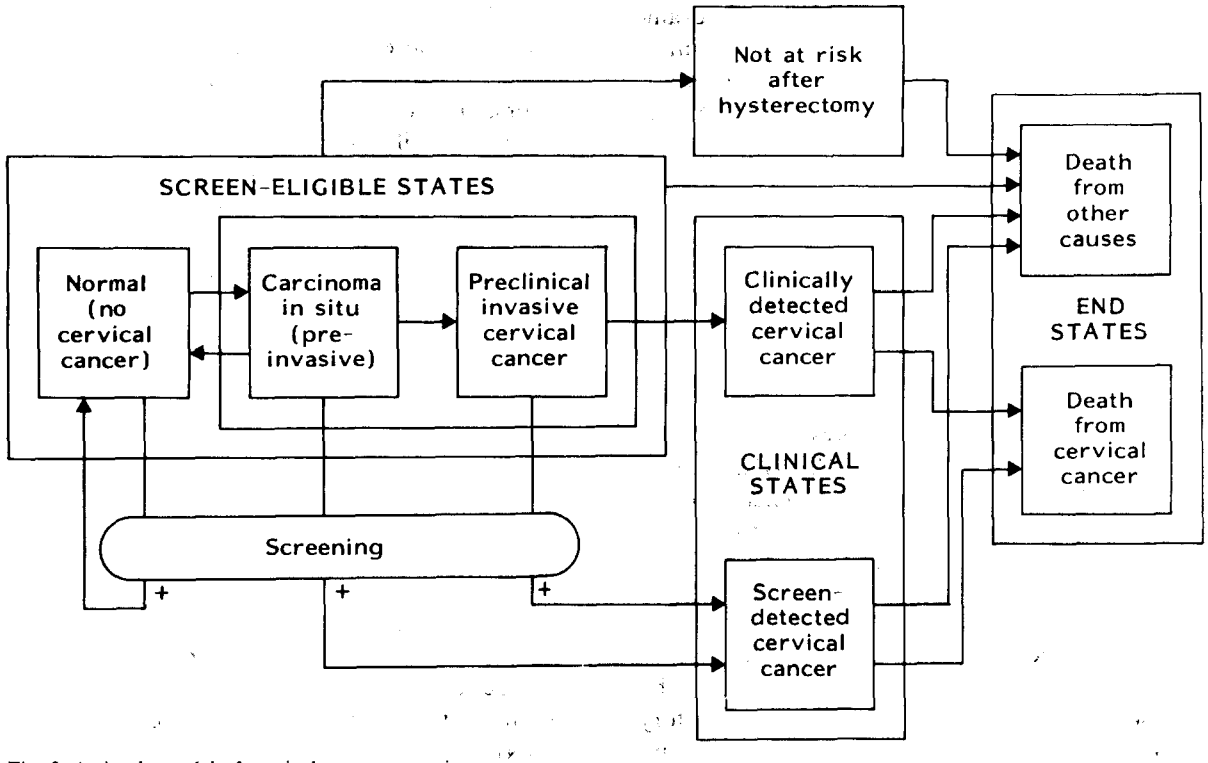

Fig. 5. A simple model of cervical cancer screening.

distribution of the dwelling time in the current state.

An alternative method of describing the transitions is by specifying competing hazards for the various subsequent disease states. This approach is described in section 3.2.5. For a mathematical treatment of both methods see the Appendix.

In simple model assumptions, the transition probabilities are assumed to have the same value for all ages. It is possible, however, to use age dependent probabilities for a transition from state i to state j, by specifying the coefficients in the following quadratic formula:

$$P_{ij}(x) = c_{ij} + c'_{ij} \cdot x + c''_{ij} \cdot x^2 \qquad (1)$$

where $P_{ij}(x)$ is the transition probability from state i to state j; x is the age at which state i has been entered; c_{ij}, c'_{ij}, c''_{ij} are coefficients determining the age dependency. When c''_{ij} is 0 there is a

TABLE 1

Hypothetical transition parameter values

Transition		Parameters		
from (i)	to (j)	c	c'	c''
NORMAL	CARCINOMA IN SITU	1	0	0
CARCINOMA IN SITU	PRECLINICAL INVASIVE	0.2	0.6×10^{-2}	0
CARCINOMA IN SITU	NORMAL	0.8	-0.6×10^{-2}	0
PRECLINICAL INVASIVE	CLINICALLY DETECTED	1	0	0
CLINICALLY DETECTED	DEATH FROM CERVICAL CANCER	0.3	0	0.6×10^{-4}

linear age dependency; age independency is obtained by $c'_{ij} = c''_{ij} = 0$.

Example. Consider the disease model for cervical cancer of Fig. 5. Hypothetical but not unrealistic values for some of the transition parameters are given in Table 1.

All cases in the example that start a disease process will first undergo a transition to state CARCINOMA IN SITU. The transition probabilities from this state depend on the age at entering the state. For example, a case entering at age 25 will have a probability of $0.2 + 0.6 \times 0.25 = 0.35$ of progression to PRECLINICAL INVASIVE, and a probability of 0.65 of returning to NORMAL. From PRECLINICAL INVASIVE, all cases progress to CLINICALLY DETECTED CERVICAL CANCER. The probability of dying from cervical cancer is age dependent, e.g. cases that are detected clinically at age 50 have a probability of $0.3 + 0.6 \times 0.5^2 = 0.45$ of dying from cancer. In the simulation, the realisation of a transition not only depends on the transition probabilities, but is also influenced by the probabilities of a transition to DEATH FROM OTHER CAUSES or NOT AT RISK, and also by the probability distribution function of the dwelling time in the state.

3.2.4. Dwelling-time distributions

The distribution of the dwelling time in the current state should be specified for each possible transition. Five distribution functions are at present implemented in MISCAN (see Table 2).

The piecewise uniform distribution can be used for specifying approximately any distribution that cannot be caught in the Erlang or Weibull function.

TABLE 2

Dwelling-time distributions implemented in the MISCAN program

Distribution	Parameters
Degenerated	Fixed dwelling time
Exponential	Mean
Weibull	Mean, shape
Erlang	Mean, rank
Piecewise uniform	$(a_1, b_1, \ldots, a_m, b_m)$

Simple model specifications will assume independence between the dwelling time in a state and the dwelling time in the previous state. It is, however, possible to define a dependency on the previous dwelling time, characterized by a parameter v, $-1 \leq v \leq +1$. Independency is indicated by $v = 0$, deterministic dependency on the previous dwelling time by $v = \pm 1$. The Appendix offers a precise mathematical description of the distributions implemented and of the dependency parameter v.

3.2.5. The competing hazards option

Transitions and dwelling times in the model should be described either by probabilistic distributions (sections 3.2.3 and 3.2.4) or by hazard rates. If the latter approach is chosen, the hazard rates should be specified for all possible transitions to new states. The actual new state results from the combined effect of these competing hazards. The hazard rates may be time dependent, i.e. depend on the time interval since the last transition. Assumptions about age dependency or dependency between subsequent dwelling times are made in the same way as for the probability distribution approach. Consult Appendix E for more details on the competing hazards option.

3.3. The screening policy

Two types of screening are implemented in the SCREENING part of MISCAN. *Mass screening* is offered systematically to a total population, or to a birth cohort of persons. People are invited by a fixed schedule, the *screening policy*, and a certain proportion, defined by the *attendance probabilities*, will accept the invitation and attend the screening. *Routine screening* takes place at irregular intervals, e.g. at the initiative of people themselves, or of their physicians. It is also possible to simulate a mixture of routine and mass screening.

3.3.1. Mass screening

Mass screening, as implemented in MISCAN, is offered either at predefined ages, or with predefined intervals between successive screenings. When simulation is restricted to a single birth cohort, all persons are invited at the same age.

When the simulation covers a population consisting of different birth cohorts, the usual assumption is that screening starts in a specific calendar year. In this case, the age of first screening will differ between the birth cohorts. Thus, the standard way of specifying a population screening schedule involves specification, for each birth cohort, of the age at which persons are invited for the first screening, and specification of the length of the intervals between the subsequent invitations to the screening. Attendance probabilities for the first screening can differ between birth cohorts, and for subsequent screenings a different attendance can be specified for each round.

Six main options are available that enable further refinements or departures from the standard specification of a mass screening policy.

I. *Recall policy.* Three different recall policies can be specified.
   1. All persons are invited to each screening round, regardless of their participation to previous screenings.
   2. Only persons who attended the previous screening round will be invited for the next round.
   3. All persons are invited for the first screening, and only the participants of this first round will be invited for the subsequent rounds. The non-attenders at the first round are not invited for second and later screenings.

II. *Attendance at first screening.* In case the population is subdivided into strata, each stratum can be assigned its own attendance probability for the first screening.

III. *Attendance at repeat screening.* Different attendance probabilities can be specified for attenders and non-attenders of the preceding screening round. A further difference between attendance probabilities can be specified for different birth cohorts and/or strata in the population.

IV. *Combination of screening tests.* Up to three different screening tests can be used (see section 3.4). For each screening round (or age in case of using option VI) it can be specified which of these tests are applied.

V. *Age at first screening.* Instead of being fixed, the age at first screening can be drawn from a probability distribution. The age distribution is either continuous, specified by giving cumulative probabilities for a number of ages, or discrete: it may be specified that the first screening takes place at one of a limited series of ages. In the latter case, a probability of first screening should be specified for each of these ages. The attendance probability can be different for different age groups or different ages, respectively.

VI. *Age at repeat screening.* It is possible to specify a series of repeat screening ages. Invitations for repeat screening will take place whenever the next age in the series is reached. This is sometimes more appropriate than assuming fixed intervals between screenings. In this option, attendance probabilities are linked to the age at repeat screening rather than to the number of the screening round.

3.3.2. Routine screening

Routine screening can be applied to both single- and multi-birth cohort populations. The ages at which screening is taking place are generated according to a probabilistic model. The following parameters of the model should be specified in case of a single birth cohort:

1. The probability of being screened at least once during a lifetime; the probability distribution of the age at first screening; and the age beyond which no further screening will take place.
2. The probability of having a second screen (for persons already screened once), and the probability distribution of the duration of the time interval between first and second screen.
3. The probability distribution of the duration of the interval between the k-th and $(k+1)$-th screen ($k \geq 2$).

Parameters (1) and (2) may differ between the strata within the population or between the cohorts in multi-cohort populations. The probability of a second screen may depend on the age at the first screen, and the probability distribution (3) may depend on the duration of the preceding interval.

3.4. Properties of the screening tests

When discussing screening tests a distinction

should be made between the preclinical disease states in which a positive result of the screening test should be interpreted as true-positive, and (preclinical) normal states, which can give rise to false-positive test results (see Fig. 4).

The probability of a positive test result in a preclinical disease state is also called the sensitivity of the screening test for that state. This probability has to be averaged over all preclinical disease states in order to obtain the overall sensitivity of the screening test. The specificity is defined in a similar way, being the probability of a negative test result in preclinical normal states.

A screening examination may consist of more than one (up to three) screening test. In case of simple model assumptions, the probability of a positive test result is taken to be independent of the results of the same tests in previous screens, and also independent of the results of other tests applied in the same or in previous screening rounds.

3.4.1. Option: Systematic test results

The assumption of independency of test results is only realistic in case false test results occur purely by chance, e.g. in case of an unnoticed technical failure. Part of the errors will occur more consistently. For example, in cancer screening, some of the tumors are missed at a screening examination because of a difficult localisation. It is highly probable that these tumors will be missed again at a subsequent screening.

The assumption of consistent errors has been implemented in the MISCAN program via the concept of systematic test results. In this concept, the results of a test have two components: one random and one systematic.

The errors in the random component occur by chance, i.e. the outcome of the test is independent of previous test results. Errors in the systematic components of test results are highly correlated. The simplest example of systematic test results occurs in cases of repeated application of a screening test to one person in a specific disease state, where all test results will be systematically negative if – and only if – the result of the first screening is so.

Although primarily implemented for false-negative test results, the concept of systematic test results as implemented in the MISCAN program can equally be used in modelling systematic true-negative outcomes, and systematic true- or false-positive outcomes.

The generalisation of systematic test results to more than one disease state and more than one screening test will not be discussed here. Although the generalisation is conceptually straightforward, the mathematical formulation is rather intricate.

3.4.2. Example

Consider a screening test with a probability of 0.30 for a false-negative test result in a preclinical disease state. When screening 800 persons in this state for the first time, the result will be positive in 560 cases, and false-negative in 240 cases. Assume that these 240 negatives stay in this disease state until the second screening. If the errors occur by chance alone, then $0.70 \times 240 = 168$ cases will be detected at the second screening, giving a total of 728 cases detected in two screening rounds. If, however, the test has a systematic false-negative component of 0.20 in this state, leaving a random component for the probability of a negative test result of 0.10, then 160 cases (2/3 of the 240 missed at the first screening) will be missed again because of a systematic error. Moreover, 10 cases $(0.10/(0.70 + 0.10) = 1/8)$ of the 80 cases that were missed because of a non-systematic error will be missed again by chance at the second screening. Thus, only 70 cases are detected at the second screening, considerably less than the 168 in case of purely random error.

3.5. Consequences of a positive test result

Positive test results can change the course of the disease without screening, as simulated in the DISEASE part of MISCAN. There are two ways of specifying such a change: as modifications relative to the original course of the disease, or as a new course independent of the original course. Changes relative to the original course focus on cases that would have died from the disease in case of no screening. The moment of death can be delayed, and the probability distribution of the length of the delay should be specified. Important special

cases of delay are complete cure (infinite delay) and no change (zero delay).

The simplest way of simulating an independent further course of the disease is by specifying survival probabilities, i.e. a probability distribution for the period between the positive test result and the time of death.

Consequences of positive test results may differ between the various disease states. They may also depend on the results of the single tests in case of more than one screening test. The options are as follows:

I. STATE CHANGE.
It can be specified that a new state (from the subset of states 'screen-detected disease', see Fig. 4) is entered at the moment of the positive test result. All states in the original course of the disease until the age of death are superceded by this new state.

II. OPERATION MORTALITY.
The probability of immediate death after a positive test result can be defined. In practice this probability can also be embedded in the survival probabilities.

III. ENTIRELY NEW COURSE OF THE DISEASE.
As an extension to the above-mentioned facility of defining (independent) new survival probabilities after a positive test result, a new or prolonged disease history can be generated by using the basic building blocks of transitions and dwelling time distributions (see section 3.2). When this option is used, a positive test result should be associated with a transition to a new state and a dwelling time distribution in this state.

4. Output of the program

The type of MISCAN output for the ANALYSIS stage of screening evaluation differs considerably from the output needed in the OPTIMIZATION stage (see Fig. 1). The most useful output for the ANALYSIS stage concerns the simulated results of the screening policy that was used in the screening project under consideration. These results are to be compared with the observed results. In the OPTIMIZATION stage, emphasis is on the simulated (positive and negative) effects of screening policies. The required output largely depends on the amount of detail that is needed in the cost–benefit calculations.

4.1. Output for the ANALYSIS stage

The output items of MISCAN for the ANALYSIS stage are listed in Table 3. The clinical incidence and mortality from the disease for an unscreened population are simulated in the DISEASE part. These simulated figures can be compared with observed incidence and mortality before the start of a screening project in the real population. The simulated results of the SCREENING part will be the most important output for the ANALYSIS stage in most applications. These results include the yield of the successive screenings of the project, the disease cases detected outside the project, and the trends in morbidity and mortality after the start of the screening. Not all disease cases will be detected by screening. For

TABLE 3

MISCAN output for the analysis stage. The most important subclassifications are indicated. Subclassification by age is relevant for all output items, as is the subclassification by birth-cohort if the population does not consist of a single cohort

DISEASE PART
a. CLINICAL INCIDENCE
Clinical incidence by disease state
b. MORTALITY DUE TO THE DISEASE
SCREENING PART
a. YIELD OF SCREENING PROJECT
Positives at first screening by disease state and by mode of detection.
Positives at repeat screening by disease state, mode of detection, rank of screening and time interval since last screening
b. DISEASE DETECTED OUTSIDE A SCREENING PROJECT
Interval cases after negative screening, by disease state, rank of screening and time interval since last screening.
Disease incidence among non-participants, by disease state.
Disease incidence in control group by disease state.
c. MORBIDITY AND MORTALITY AFTER SCREENING
Clinical incidence in study- and control-population, by disease state.
Disease mortality in study- and control-population.
Survival in different subgroups.

participants to the screening, the disease can be missed because of a false-negative test result, or because of the fast progress of the disease in the interval between two screenings. Especially the results of the subsequent screenings and the number of interval cases diagnosed between screenings are important in testing assumptions about the underlying process. The testing consists of an appraisal of the goodness-of-fit between the observed results from an existing screening project and the simulated results.

If the fit is reasonably good, it is concluded that the input assumptions, from which the simulated results are computed, are compatible with the observed results of the project (see Fig. 1). Other simulation results, such as simulated attendance figures or the simulated age-specific death from other causes, are useful for the control of input specifications. Some MISCAN output gives insight into the natural history of the disease and other phenomena that are not directly observable in reality, e.g. the simulated prevalence of the preclinical states of the disease, the mean lead time for screen-detected cancers, and the state distribution of cancers with a false-negative test result.

4.2. Output for the OPTIMIZATION stage

In the OPTIMIZATION stage of using MISCAN, many different screening policies are simulated. The results of these simulations are subsequently used in cost–benefit or cost-effectiveness calculations. The aim of these calculations is to find the policies with highest net benefit or highest cost-effectiveness. A problem in the optimization is that it involves comparison of such heterogeneous effects as financial costs, increased life expectancy, and anxiety caused by a (possibly incorrect) positive test result. Simulated effects that should be considered for inclusion in a cost–benefit analysis are listed in Table 4. The output from the DISEASE part can be used as a baseline when computing the relative effectiveness of screening. In comprehensive cost–benefit analyses, more data will be needed, possibly from the output listed in Table 3 (e.g. the shift in stage distribution caused by screening can serve as an indicator for a relative increase of less extensive treatment as a result of screening).

TABLE 4

MISCAN output for the optimization stage

DISEASE PART
Lives and life-years lost by disease
SCREENING PART
Lives saved by screening
Life-years gained by screening
Life-years without disease gained or lost by screening
Number of false-positive test results
Number of unnecessarily treated persons
Number of disease cases induced by screening
Number of persons invited for screening
Number of screenings actually performed

Note that the number of screenings may be used as a proxy for a number of important items, e.g. financial costs of screening, time needed by the participants, anxiety while waiting for the screening result, etc.

5. Discussion

5.1. Other models for evaluation of screening

A number of other models for simulation of mass screening for cancer have been described. Especially carefully developed are the models proposed for bladder cancer by Ellwein [6], the breast cancer model of Shwartz [5], and the general (disease independent) models by Knox [3], Walter and Day [7] and Eddy [4]. A review of the modelling approach has been given by Eddy and Shwartz [2].

None of these models uses a microsimulation approach. Eddy, Shwartz and Walter and Day use computer programs that numerically solve the integral equations of their model description. The models of Knox and Ellwein are implemented in computer programs that are based on macrosimulation, i.e. the probability of compound events is obtained by multiplication and aggregation of probabilities of component events.

Different types of restriction and limitations are posed by these simulation methods. The numerical method requires that the models are not too complex, thus making simplifying assumptions inevitable. When macrosimulation is used, the number of

(inter)dependencies between variables in the model should be restricted, and again simplifying assumptions are required for most applications.

In principle, such limitations do not exist for the microsimulation method. This makes MISCAN a powerful method, especially for the ANALYSIS stage of evaluation. The generality of the approach is illustrated by the fact that MISCAN can easily simulate earlier general models [3,4,7]. The 'disease-specific' models of Shwartz and Ellwein, in which some characteristic features of the disease are implemented (e.g. exponential tumor growth for breast cancer) can also be simulated, if some minor adaptations are made. The capability of simulating either models has been used during the development of MISCAN to check the correctness of simulated results, mainly by comparison with Knox's SCRMOD program [3].

However, a price has to be paid for the possibility of more detailed modelling. Monte Carlo simulation needs much computer time and relatively more manpower. Of course, when compared to the total costs of screening and the possible financial and health benefits of switching to a better screening policy, the extra costs of using the microsimulation approach of the MISCAN program are negligible.

3.2. Applications

Thus far, MISCAN has been used in the evaluation of breast cancer screening and cervical cancer screening [8–10]. For breast cancer, the (randomized) HIP study [11] has been simulated and (preliminary) attempts have been made to simulate the current screening projects that make use of the more sensitive and less risky modern mammography. For cervical cancer, the screening program in British Columbia [12] has been simulated. For breast cancer as well as for cervical cancer, the approach outlined in Fig. 1 has been followed. First, assumptions about the underlying process have been tested (analysis stage), and confidence intervals for various parameters of the respective underlying processes have been derived. Then, a cost–benefit investigation has been carried out (optimization stage): optimal screening policies have been derived for a number of different cost–benefit trade-offs.

The MISCAN program, although explicitly designed for simulation of screening for cancer, may prove to be of use in other fields of research, e.g. in experimental pathogenesis and in evaluation of risk factors and interventions for other diseases, including multifactorial dose–response studies.

3.3. Implementation

The current version of MISCAN is written in FORTRAN. The source listing comprises about 10,000 lines, 2,500 for the DISEASE part and 7,500 for the SCREENING part. No use is made of library routines or assembler routines. Running on a DEC 20/60 mainframe, the executable programs have a size of 140 Kbytes (DISEASE part) and 265 Kbytes (SCREENING part). When using both parts, about 2 Mb of memory is needed to store life histories and program output. Simulation of an adequate number of life histories takes about 10–60 s for the DISEASE part, and 30 s to about 5 min for the SCREENING part. The actual time needed will depend largely on the complexity of the disease process, and for the SCREENING part also on the number of screenings that have to be simulated.

Acknowledgements

The development of the MISCAN evaluation approach was made possible by grants no. 500 and 28-935 from the 'Praeventiefonds' (Prevention Fund) and by grant no. EUR-EP79-5 of the 'Koningin Wilhelmina Fonds' (Netherlands Cancer Foundation).

References

[1] J.D.F. Habbema, G.J. van Oortmarssen and P.J. van der Maas, Mass screening for cancer: the interpretation of findings and the prediction of effects on morbidity and mortality, Clin. Lab. Med. 2 (1982) 627–638.

[2] D.M. Eddy and M. Shwartz, Mathematical models in screening, *in*: Cancer Epidemiology and Prevention, eds. D. Schottenfeld and J.F. Fraumeni, pp. 1075–1090 (W.B. Saunders, Philadelphia, 1982).

[3] E.G. Knox, A simulation system for screening procedures, *in*: The Future and Present Indicatives, ed. G. McLachlan, pp. 19–55 (Nuffield Prov. Hosp. Trust, London, 1973).
[4] D.M. Eddy, Screening for Cancer: Theory, Analysis, and Design (Prentice–Hall, Englewood Cliffs, 1980).
[5] M. Shwartz, A mathematical model used to analyse breast cancer screening strategies, Operations Res. 26 (1978) 937–955.
[6] L.B. Ellwein, Bladder Cancer with Intervention. A computerized simulation model (Science Applications, La Jolla, CA, 1978).
[7] S.D. Walter and N.E. Day, Estimation of the duration of a preclinical disease state using screening data, Am. J. Epidemiol. 118 (1983) 865–886.
[8] J.D.F. Habbema, J.Th.N. Lubbe, P.J. van der Maas and G.J. van Oortmarssen, A computer simulation approach to the evaluation of mass screening, *in*: MEDINFO 83. Proceedings of the 4th world conference on medical informatics, eds. J.H. van Bemmel, M.J. Ball and O. Wigertz, pp. 1222–1225 (North-Holland, Amsterdam, 1983).
[9] J.D.F. Habbema, J.Th.N. Lubbe, P.J. van der Maas and G.J. van Oortmarssen, Het MISCAN model: Een Nieuwe Methode voor Evaluatie van Bevolkingsonderzoek. Deel I: Bevolkingsonderzoek op Baarmoederhalskanker (Technical Report, Dept. of Public Health and Social Medicine, Erasmus University, Rotterdam, 1982).
[10] J.D.F. Habbema, D.J. van Putten, J.Th.N. Lubbe, P.J. van der Maas and G.J. van Oortmarssen, Het MISCAN model: Een Nieuwe Methode voor Evaluatie van Bevolkingsonderzoek. Deel II: Bevolkingsonderzoek op Borstkanker (Technical Report, Dept. of Public Health and Social Medicine, Erasmus University, Rotterdam, 1983).
[11] S. Shapiro, W. Venet, P. Strax, L. Venet and R. Roesner, Ten- to fourteen-year effect of screening on breast cancer mortality, JNCI 69 (1982) 349–355.
[12] D.A. Boyes, B. Morrison, E.G. Knox, G.J. Draper and A.B. Miller, A cohort study of cervical cancer screening in British Columbia, Clin. Inv. Med. 5 (1982) 1–29.

Appendix

A. Transitions and dwelling times

The finite set E consists of all states of the disease process. A life history is represented by a sequence of pairs (X_k, Y_k), $(k = 1, 2, 3, \ldots)$, where $Y_k \in E$ represents the k-th state and $X_k \geq 0$ the age at entering Y_k ($Y_1 =$ 'normal', $X_1 = 0$). The length of the dwelling time in the k-th state Y_k is indicated by $T_k = X_{k+1} - X_k$.

A new pair (X_{k+1}, Y_{k+1}) can be simulated in two different ways. The standard way is that the new state Y_{k+1} is determined first, from transition probabilities. Then, a dwelling time T_k is computed from a dwelling time distribution whose parameters may also depend on the new state Y_{k+1}.

An alternative way of determining a new (age, state) pair is offered by the competing hazard option. In this case, hazard functions for a transition to each of the possible new states should be specified. Dwelling times are simulated for each of the possible transitions, and the state which corresponds with the shortest dwelling time will become the new X_{k+1}.

New pairs of 'age of entry' and 'disease state entered' for the disease process are simulated until the disease process is terminated. This may happen in three ways: by reaching the simulated age of death from other causes, by reaching the (optional) age at which the NOT AT RISK state is entered, or by entering an end (absorbing) state of the disease process (e.g. the state DEATH FROM DISEASE).

B. Transitions

The sequence of states $Y_1, Y_2, Y_3, \ldots$ is assumed to be a markov chain, with transition matrix P. Element (i, j) of P is indicated by P_{ij}. In simple applications, P_{ij} does not depend on age x:

$$P_{ij} = Pr\{Y_{k+1} = j \mid Y_k = i\}$$

$$i, j \in E; \quad k = 1,2,3,\ldots \tag{A1}$$

Age dependency of the transition probabilities can be introduced by stating:

$$P_{ij}(x) = Pr\{Y_{k+1} = j \mid Y_k = i, X_k = x\}$$

$$i, j \in E; \quad k = 1,2,3\ldots; \; x \geq 0 \tag{A2}$$

The following 3-parameter function is implemented for the modelling of age dependency:

$$P_{ij}(x) = c_{ij} + c'_{ij} \cdot x + c''_{ij} \cdot x^2 \tag{A3}$$

C. Dwelling times

The duration $T_k = X_{k+1} - X_k$ of the dwelling time in state $Y_k = i$, when the next state is known

to be $Y_{k+1} = j$, is distributed according to a probability distribution function $Q_{ij}(t)$. In simple applications, this function is independent from the preceding dwelling time T_{k-1}, and depends only on the current state Y_k and the next state Y_{k+1}:

$$Q_{ij}(t) = Pr\{T_k \leqslant t | Y_{k+1} = j, Y_k = i\}$$

$$i, j \in E;\ t \geqslant 0;\ k = 1,2,\ldots \qquad \text{(A4)}$$

A number of probability distribution function types are available in MISCAN (see Table 1).

(1) Erlang distribution:

$$Q(t) = 1 - \exp(-a \cdot t) \cdot \sum_{i=0}^{b-1} (a \cdot t)^i/(i!)$$

$$a > 0;\ t \geqslant 0;\ b = 1,2,\ldots \qquad \text{(A5)}$$

mean: b/a; variance: b/a^2.

(2) Weibull distribution:

$$Q(t) = 1 - \exp\{-(t/b)^c\} \qquad b > 0;\ c > 0;\ t \geqslant 0 \qquad \text{(A6)}$$

mean: $b \cdot \Gamma(1 + 1/c)$; variance: $b^2 \cdot \{\Gamma(1 + 2/c) - (\Gamma(1 + 1/c))^2\}$ ($\Gamma(x)$ indicates the gamma function)

The exponential distribution is a special case of the Erlang distribution ($b = 1$) or the Weibull distribution ($c = 1$).

(3) Piecewise uniform distribution:

Parameters: $0 = a_1 \leqslant a_2 \leqslant a_3 \ldots \leqslant a_m = 1$ (probabilities)
$0 \leqslant b_1 \leqslant b_2 \leqslant b_3 \ldots \leqslant b_m$ (dwelling times)

$$Q(a_i) = b_i \quad i = 1,2,\ldots,m. \qquad \text{(A7)}$$

(4) Degenerate distribution: the dwelling time is fixed and equal to a:

$$Pr\{T = a\} = 1 \quad a \geqslant 0. \qquad \text{(A8)}$$

D. Association between dwelling times

The probability distribution function of dwelling time T_k should sometimes be made dependent on the previous dwelling time T_{k-1}:

$$Q_{ij}(t, s) = Pr\{T_k \leqslant t | Y_{k+1} = j, Y_k = i, T_{k-1} = s\}$$

$$i, j \in E;\ s \geqslant 0;\ t \geqslant 0;\ k = 2,3,\ldots \qquad \text{(A9)}$$

In simulation, two subsequent dwelling times T_{k-1} and T_k, with probability distribution functions $F(t)$ and $G(t)$ respectively, are associated if the random numbers $r_{k-1} = F(T_{k-1})$ and $r_k = G(T_k)$ are associated. In MISCAN this association is characterized by the parameter v, $-1 \leqslant v \leqslant +1$.

r_k is calculated as the weighted average of r_{k-1} and a newly drawn true random number r, $0 < r < 1$:

$$r_k = \begin{cases} (1 - v) \cdot r + v \cdot r_{k-1} & 0 \leqslant v \leqslant 1 \\ (1 + v) \cdot r - v \cdot (1 - r_{k-1}) & -1 \leqslant v \leqslant 0 \end{cases} \qquad \text{(A10)}$$

In this way, a fractile-based dependency measure is obtained. The dwelling time T_k is now computed from the probability distribution function in the way described before. For Erlang distributions with $b > 1$, an approximate for this procedure is used.

E. Competing hazards

Let $Y_k = i$ be a state entered at age $X_k = x$. Then hazards (instantaneous transition rates) can be specified for transitions to any of the other states. The hazards for transitions to different states are mutually independent. In MISCAN hazards are assumed to be 'piecewise constant', i.e. constant over dwelling time intervals denoted by (b_u, b_{u+1}), and can (optionally) be dependent from the age $X_k = x$ in a way similar to the age dependency of transition probabilities. In general, the hazard $h_{ij}(x, t)$ for a transition to state j after a dwelling time t since the age x at entering current

state i is parametrized as follows:

$$h_{ij}(x, t) = d_{iju} \cdot \left(c_{ij} + c'_{ij} \cdot x + c''_{ij} \cdot x^2\right)$$

$$b_u < t \leqslant b_{u+1};\ i, j \in E;\ u = 1,2,3,\ldots \tag{A11}$$

The corresponding accumulated hazard after time t equals:

$$H_{ij}(x, t) = \int_0^t h_{ij}(x, y)\mathrm{d}y \tag{A12}$$

If there was only the possibility of transition to state j ($h_{im} = 0$ for all $m \neq j$, $m \in E$) then the probability distribution for the dwelling time T_k is:

$$Pr\{T_k(j) \leqslant t\} = 1 - \exp\{-H_{ij}(x, t)\} \tag{A13}$$

The dwelling time $T_k(j)$ is generated by solving this equation, where the probability is replaced by random number r_{kj}, $0 < r_{kj} < 1$:

$$r_{kj} = 1 - \exp(-H_{ij}(x, t)) \tag{A14}$$

If hazards for transitions to all other states are taken into account, for each state j a random number r_{kj} can be used to find dwelling times $T_k(j)$, and the combined effect of all hazards is that the next state Y_{k+1} and the next dwelling time T_k will be:

$$Y_{k+1} = \{j | \forall m \in E : T_k(j) \leqslant T_k(m)\} \tag{A15}$$

$$T_k = \min_{j \in E} T_k(j) \tag{A16}$$

The age X_{k+1} at transition to Y_{k+1} is simply computed from:

$$X_{k+1} = X_k + T_k \tag{A17}$$

The dependency of dwelling times in subsequent states in a disease process is extended to the hazards, still using the same random number adaptation method (A10). In computing a dwelling time $T_k(j)$ from the hazards specified, each random number r_j used will depend on the random number r_{k-1}. Once the minimal dwelling time T_k has been determined, the value of the probability distribution function for $T_k = t$ is computed:

$$Pr\{T_k \leqslant t\} = 1 - \prod_{j \in E} \left(1 - Pr\{T_k(j) \leqslant t\}\right)$$

$$= 1 - \exp\left\{\sum_{j \in E} - H_{ij}(x, t)\right\} \tag{A18}$$

This value is used at subsequent transitions as if this were the random number that has been used to compute T_k.