Simulation of Populations in a Time-, Age- and Duration Dependent Illness-Death Model

Ralph Brinks
German Diabetes Center
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Abstract
Relevant events in a three state illness-death model (IDM) of a chronic disease are the diagnosis of the disease and death with or without the disease. In this article a simulation framework for populations moving in the IDM is presented. The simulation is closely related to the concept of Lexis diagrams in event history analysis. Details of the implementation and an example of a hypothetical disease are described.

Keywords: current status data, simulation, Lexis diagram, Siddon’s algorithm

1 A simple illness-death model

A popular framework for studying irreversible diseases is the illness-death model (IDM) consisting of three states as depicted in Figure 1: Normal, Disease and Death (Keiding 1991, Kalbfleisch and Prentice 2002, Aalen, Brogan, and Gjessing 2008). The associated transition rates are denoted with the symbols as in Figure 1: incidence $i$, and mortality rates $m_0$ and $m_1$. In general, the rates depend on different time scales: calendar time $t$, age $a$ and in case of $m_1$ on the duration $d$ of the disease.

In this article a framework for simulating populations moving in the IDM is presented. For each person $j$, $j = 1, \ldots, n$ in the population, the relevant events diagnosis and death are simulated. This is accomplished in two steps:

1. Contracting the disease and dying without the disease is modelled as competing risk. Given the time $t_0^{(j)}$ of birth of person $j$, the cumulative

\footnote{ synonymously: densities (in units “per person-year”, not to be confused with risks or probabilities (Vandenbroucke and Pearce 2012).}
Figure 1: Three states model of normal, diseased and dead subjects. Transition densities may depend on calendar time \( t \), age \( a \), and in case of \( m_1 \) also on the duration \( d \) of the disease.

The term “first failure time” \( T_1^{(j)} \) refers to the time of diagnosis or death without disease. \( T_1^{(j)} \) is measured in time units after birth of person \( j \). Thus, \( T_1^{(j)} \) is the age when the first transition from the state Normal occurs. Assumed we know that for person \( j \) at \( T_1^{(j)} \) a transition occurs, then the odds of transiting into state Disease versus transiting into state Death is

\[
\frac{i(t_0^{(j)} + T_1^{(j)}, T_1^{(j)})}{m_0(t_0^{(j)} + T_1^{(j)}, T_1^{(j)})}.
\]

2. If the event at \( T_1^{(j)} \) is the death (without the disease), the simulation for person \( j \) is finished. If, however, the event is the diagnosis of the disease, the “second failure time” \( T_2^{(j)} \) to death (with disease) has the distribution function \( F_2^{(j)} \):

\[
F_2^{(j)}(t | T_1^{(j)}) = 1 - \exp \left( - \int_0^t m_1(t_0^{(j)} + T_1^{(j)} + \tau, T_1^{(j)} + \tau, \tau) \, d\tau \right).
\]

The next section describes in detail how the integrals in Eqs. 1 and 3 are calculated in the implementation of the simulation. After calculating the integrals, the question arises how the times \( T_1 \) and \( T_2 \) can be obtained from \( F_1 \) and \( F_2 \). This is done by the inverse transform sampling method:
Let $F$ be a cumulative distribution function and $u \in (0, 1)$. For $F^{-1}(u) := \inf \{x \mid F(x) \geq u\}$, it holds: If $U$ is a uniform random variable on $(0, 1)$, then $F^{-1}(U)$ follows the distribution $F$. Thus, the simulation of $T_1$ and $T_2$ is easy, if a random number generator for $U$ such as runif in R is available.

For each of the $n$ persons in the population we store four pieces of data:

1. a unique identifier $j$,
2. the date $t_0^{(j)}$ of birth (dob) of person $j$,
3. the age at diagnosis (adi) of person $j$, and
4. the age of death (ade) of person $j$.

If the person $j$ does not contract the disease, the age at diagnosis $adi$ is set to NA (missing).

In summary, we get the following

\begin{algorithm}
\begin{algorithmic}
\State \textbf{for} $j = 1 \to n$ \textbf{do}
\State \hspace{1em} dob $\leftarrow t_0^{(j)}$
\State \hspace{1em} calculate event time $T_1^{(j)}$ according to Eq. (1)
\State \hspace{1em} simulate type of event that has happened at $T_1^{(j)}$ by Eq. (2)
\State \hspace{1em} if event is diagnosis then
\State \hspace{2em} adi $\leftarrow T_1^{(j)}$
\State \hspace{2em} calculate time $T_2^{(j)}$ of death using Eq. (3)
\State \hspace{2em} ade $\leftarrow T_1^{(j)} + T_2^{(j)}$
\State \hspace{1em} else
\State \hspace{2em} adi $\leftarrow$ NA
\State \hspace{2em} ade $\leftarrow T_1^{(j)}$
\State \hspace{1em} end if
\State \hspace{1em} write $j$, dob, adi, ade to file
\State \textbf{end for}
\end{algorithmic}
\end{algorithm}

This allows us to define the file format for storing the results of Algorithm 1. For each person $j$ the four entries $j$, dob, adi, ade stored in a row of an ASCII text file. Delimiter between the four entries are semicolons (;), decimal separators are dots (.). The file extension is spd (simulation of populations moving in the illness-death model).

A few words are devoted to the applications and benefits, such a simulation has. The motivation for the algorithm comes from analytical epidemiology.
where relations between common epidemiological measures are studied. Examples for those measures are the prevalence, the duration of a disease, the age of onset or diagnosis, and lost life years (due to the disease). Obviously, the characteristics of the age of diagnosis can be obtained directly from the simulation. A typical question in that respect may be: what is the mean age of diagnosis of those subjects born between $t_s$ and $t_e$? Another interesting aim is the estimation of the incidence rate $i$ from cross-sectional information. At a specific point in time $t'$, each of the subjects $j = 1, \ldots, n$, has a unique “status”. Neglecting those who are unborn or dead at $t'$, the status is either normal (non-diseased) or diseased. Thus, the status can be seen as a binary random variable, and data of this kind is typically called current status data. The current status is closely linked with the incidence $i$ and the mortalities $m_0$ and $m_1$. Estimating the incidence from current status data, for example, has been a topic in research for decades (Hens, Aerts, Faes, Shkedy, Lejeune, van Damme, and Beutels 2010). The framework presented here may be useful in this field.

2 Line integrals in the Lexis diagram

In this section the calculation of the integrals in Eqs. (1) and (3) are described. Since we are interested in integrating arbitrary integrands $i$, $m_0$, and $m_1$, we use numerical integration. We assume that the integrands are given by numerical values on a regular grid. In event history analysis (Keiding 2006), a useful concept is the Lexis diagram, which is a co-ordinate system with axes calendar time $t$ (abscissa) and age $a$ (ordinate). The calendar time dimension sometimes is referred to as period. Each subject is represented by a line segment from time and age at entry to time and age at exit. Entry and exit may be birth and death, respectively, or entry and exit in a epidemiological study or clinical trial. There are excellent and extensive introductions about the theory of Lexis diagrams (see for example (Keiding 1990, 1991; Carstensen 2006) and references therein), which allows to be short here. When it comes to irreversible diseases, the commonly used two-dimensional Lexis diagram with axes in time and age direction may be generalized to a three-dimensional co-ordinate system with disease duration $d$ represented by the applicate (z-axis). If a subject does not get the disease during life time, the life line remains in the time-age-plane parallel to the line bisecting abscissa and ordinate. With other words, the life line for the time without disease is parallel to $e_1 := (1, 1, 0)^t$ (where the triple $(t, a, d)$ denotes the co-ordinates in time, age and duration direction, respectively). However if at a certain point in time $E$ the disease is diagnosed, the life line changes its direction, henceforth parallel to $e_2 := (1, 1, 1)^t$. The situation is illustrated in Figure 2. The life lines of two subjects are shown in the three-dimensional Lexis space. At time of birth (denoted $B_\nu$, $\nu = 1, 2$) both
subjects are disease-free; both life lines are parallel to \( e_1 \). The first subject gets the disease at \( E \), and henceforth the life line is parallel to \( e_2 \) until death at \( D_1 \). The second subject remains without the disease for the whole life, which ends at \( D_2 \).

Figure 2: Three-dimensional Lexis diagram with two life lines. Abscissa, ordinate and applicate represent calendar time \( t \), age \( a \) and duration \( d \), respectively. The life lines start at birth \( B_\nu \) and end at death \( D_\nu \), \( \nu = 1, 2 \). The first subject gets the disease at \( E \). Then, the life line changes its direction. The second subject does not get the disease, the corresponding life line remains in the \( t-a \)-plane.

Having the concept of the Lexis diagram at hand, we observe that \( F_1 \) and \( F_2 \) in Eqs. \( \text{(1)} \) and \( \text{(3)} \) are line integrals in the Lexis space. We start with calculating the first failure times \( T_1 \). For subject \( j \) the associated life line starts at \( (t, a) = (t_0^{(j)}, 0) \). We chose an age \( \omega > 0 \), when it is sure that a transition to one of the states Disease or Death has occurred, say \( \omega = 150 \) (years). For calculating \( F_1^{(j)} \), we trace the hypothetical life line from \( B_j := (t_0^{(j)}, 0) \) to \( D_j := (t_0^{(j)} + \omega, \omega) \). Thus, the hypothetical life line has a representation

\[
\mathcal{L}_j : \quad B_j + \alpha \cdot (D_j - B_j), \quad \alpha \in [0, 1].
\]

As described in [Brinks 2012] following the life line is related to raytracing in the field of computer graphics, where efficient algorithms for this purpose exist. In Siddon’s algorithm [Siddon 1985], the key idea is to follow \( \mathcal{L}_j \) by calculating intersections with volume elements (voxels), which form a regular partition of the Lexis space. Let

\[
A_j^* = \{ \alpha^{(j)}(p) \mid p = 1, \ldots, P^{(j)} \}
\]
with $0 = \alpha^{(j)}(1) < \cdots < \alpha^{(j)}(P^{(j)}) = 1$ be a parametrization of the points where $L_j$ intersects the voxel faces plus the start and end points $B_j$ and $D_j$. Details for the calculation of $A_j^*$ are described in Brinks (2012). The parametrization $A_j^*$ is ideally suited for approximating the integral in Eq. (11) by the trapezoidal rule (Dahlquist and Björck 1974). The reason lies in the fact that in calculating $F_1^{(j)}(\omega)$ the values $F_1^{(j)}(t_0^{(j)} + \alpha^{(j)}(p) \omega)$, $p = 1, \ldots, P^{(j)}$, are a byproduct. Algorithm 2 shows the necessary steps.

Algorithm 2 Calculating $F_1$

1: for $j = 1$ to $n$ do
2: Calculate $A_j^* = \{\alpha^{(j)}(p) \mid p = 1, \ldots, P^{(j)}\}$.
3: $\ell_1 \leftarrow 0$
4: $\tau_1 \leftarrow 0$
5: $f_1 \leftarrow i\left(t_0^{(j)}, 0\right) + m_0 \left(t_0^{(j)}, 0\right)$
6: $F_1^{(j)}(\tau_1) \leftarrow 0$
7: for $p = 2$ to $P^{(j)}$ do
8: $\tau_p \leftarrow \alpha^{(j)}(p) \cdot \omega$
9: $f_p \leftarrow i\left(t_0^{(j)} + \tau_p, \tau_p\right) + m_0 \left(t_0^{(j)} + \tau_p, \tau_p\right)$
10: $\ell_p \leftarrow \ell_{p-1} + \frac{1}{2} \cdot (\tau_p - \tau_{p-1}) \cdot (f_p + f_{p-1})$
11: $F_1^{(j)}(t_0^{(j)} + \tau_p) \leftarrow 1 - \exp(-\ell_p)$
12: end for
13: end for

Since the values of $i$ and $m_0$ are given on the voxel grid only, the calculation of $f_p$, $p = 1, \ldots, P^{(j)}$, needs bilinear interpolation of the values of the adjacent voxels (Press, Flannery, Teukolsky, and Vetterling 1988).

After preparing $F_1^{(j)}$, $j = 1, \ldots, n$, the times $T_1^{(j)}$ can be calculated by the inverse transform sampling method. Since we have $F_1^{(j)}$ calculated at points $\zeta_p := t_0^{(j)} + \tau_p$, $p = 1, \ldots, P^{(j)}$, the inverse transform sampling would yield only those $\zeta_p$. A better accuracy can be obtained by interpolating $F_1^{(j)}$ affine-linearly between consecutive $\zeta_p$. For $t \in (\zeta_{p-1}, \zeta_p)$, $p = 2, \ldots, P^{(j)}$, let $\xi := \frac{t - \zeta_{p-1}}{\zeta_p - \zeta_{p-1}}$. Then, it holds

$$F_1^{(j)}(t) \approx (1 - \xi) \cdot F_1^{(j)}(\zeta_{p-1}) + \xi \cdot F_1^{(j)}(\zeta_p).$$

For those subjects $j'$ who contract the disease, the associated $F_2^{(j')}(\cdot \mid T_1^{(j')})$ can be derived in a similar way as in Algorithm 2. The associated line segment starts at $(t, a, d) = (t_0^{(j')}, T_1^{(j')}, T_1^{(j')}, 0)$. Again, a hypothetical maximal disease duration $\omega'$ is assumed, say $\omega' = 50$ (years), such that the line segment ends at $(t, a, d) = (t_0^{(j')}, T_1^{(j')} + \omega', T_1^{(j')} + \omega', \omega')$. Thus, the
line segment is parallel to $e_2 = (1, 1, 1)^t$. The Siddon algorithm computes the corresponding set of intersections with the voxel grid accordingly. The ages $T_{d_j}^{(j)}$ of death with disease are obtained from Algorithm 2 mutatis mutandis. The interpolation of $m_1$ needs to be trilinear.

3 Example

This section presents the results of a simulation. In each of sixty consecutive years $t = 0, \ldots, 59$, two hundred persons are born and followed from birth to death. The incidence of a hypothetical chronic disease is assumed to be $i(t, a) = \frac{(a-30)+3000}{3000}$, the mortality of the non-diseased is $m_0(t, a) = \exp(-10.7 + \ln(0.998) + 0.1a + t \ln(0.998))$ and the mortality of the diseased is $m_1(t, a, d) = m_0(t, a) \cdot (0.04(d-5)^2 + 1)$. In total, 4184 of the 12000 simulated persons contract the disease. The simulated data easily allows derivation of important epidemiological measures. For example, the histograms of the age at onset and age at death are shown in Figure 3.

![Histograms](image.png)

Figure 3: Histograms of the age at onset (left) and age at death (right) in the simulation.

The median age at death of those who contracted the disease is 77.3 (years) whereas the median age at death of those without the disease is 79.6 (years). The mean duration of the disease in the 4184 ill subjects is 12.5 (years).

To cross-check the results of the simulation, we compare them to a theoretical calculation. In year $t = 100$, exactly 7368 persons are alive, 799 having the hypothetical disease. Figure 4 shows the age-specific prevalence in the year 100. The black lines indicate the prevalence of several age groups together with 95% confidence bounds as given by the simulation. The blue
line represents the prevalence calculated analytically by the exact formula in [Keiding 1991, Section 7.2]. The results agree quite well within the confidence bounds.

Figure 4: Simulated (black) and analytically calculated (blue) prevalence of a hypothetical disease. The simulated prevalence is depicted with 95% confidence intervals.

4 Summary

This article is about simulating populations in an illness-death model consisting of the three states Normal, Disease, and Death. The disease is assumed to be irreversible. After birth of an subject in the population, two cases may occur:

1. the subject dies without the disease, or
2. the subject contracts the disease and dies with the disease.

In the first case, the life lines of the Lexis diagram are solely located in the $t-a$-plane parallel to $e_1 = (1, 1, 0)^t$. In the second case, a part of the life lines is parallel to the $e_2 = (1, 1, 1)^t$ direction. Changing the direction of the life line allows modelling the covariable duration of the disease. In many diseases,
the duration plays an important role for the mortality. Examples are diseases related to arteriosclerosis such as diabetes (Carstensen, Kristensen, Ot-tosen, and Borch-Johnsen 2008) or lupus erythematosus (Bernatsky, Boivin, Joseph, Manzi, Ginzler, Gladman, Urowitz, Fortinand, Petri, Barr, Gordon, Bae, Isenberg, Zoma, Aranow, Dooley, Nived, Sturfelt, Steinsson, Alarcón, Senécal, Zummer, Hanly, Ensworth, Pope, Edworthy, Rahman, Sibley, El-Gabalawy, McCarthy, Pierre, Clarke, and Ramsey-Goldman 2006).

The simulation is based on raytracing techniques and provides a fast way to follow the individual life lines of subjects in the Lexis diagram. Computation time is an issue, because the number of subjects may be large (several thousands). The simulation calculates event times (diagnosis of the disease or death) and uses inverse transform sampling via cumulative distribution functions. The integrals occurring in the distribution functions are approximated by the trapezoidal rule of numerical integration, which ideally fits to the raytracing technique.

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Ralph Brinks
Institute for Biometry & Epidemiology
German Diabetes Center
D-40225 Düsseldorf, Germany
E-mail: ralph.brinks@ddz.uni-duesseldorf.de