Partial differential equation about the prevalence of a chronic disease in the presence of duration dependency

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Abstract

The illness-death model of a chronic disease consists of the states Normal, Disease, and Death. In general, the transition rates between the states depend on three time scales: calendar time, age and duration of the chronic disease. Previous works have shown that the age-specific prevalence of the chronic disease can be described by differential equations \[2, 4\] if the duration is negligible. This article derives a partial differential equation (PDE) in the presence of duration dependency. As an important application, the PDE allows the calculation of the age-specific incidence from cross-sectional surveys.

1 Introduction

The articles \[2\] and \[4\] deal with the illness-death model as shown in Figure 1. The model describes a population consisting of healthy and ill persons with respect to a chronic (i.e., irreversible) disease. Let the number of persons in the states Normal and Disease be denoted with \(S\) and \(C\). The transition rates between the states are the incidence rate \(i\) and the mortality rates \(m_0\) and \(m_1\) of the healthy and the diseased persons, respectively. In general, these rates depend on the calendar time \(t\), on the age \(a\) and in case of \(m_1\) also on the duration \(d\).

The articles \[2\] and \[4\] derived differential equations (DEs) about the age-specific prevalence \(p = \frac{C}{C+S}\) and the rates \(i, m_0\) and \(m_1\):

\[
\partial p = (1 - p) \left( i - p (m_1 - m_0) \right).
\]

The symbol \(\partial\) means a differential operator, either \(\partial = \frac{\partial}{\partial a}\) or \(\partial = \frac{\partial}{\partial t} + \frac{\partial}{\partial a}\), depending on the setting.
Figure 1: Illness-death model with three states and the associated transition rates. Persons in the state *Normal* do not have the chronic disease. In case of an onset, they change to the state *Disease*.

The advantages of an equation of the form (1) is the relatively simple relation between the rates $i, m_0, m_1$ and the prevalence $p$. If the rates on the right hand side of the equation are known, the DE can be solved for $p$. This is called the *direct problem*. Furthermore, if $p, m_0$ and $m_1$ are known, Equation (1) can be solved for the incidence $i$. This *inverse problem* allows the calculation of the incidence of a chronic disease from cross-sectional data. Usually in epidemiology, incidence rates are surveyed by lengthy (and thus expensive) follow-up studies. The possibility to use less complex cross-sectional data instead of follow-up studies is an enormous benefit and has been requested for a long time (see [7] for an overview).

The DEs in [2,4] were restricted to the case of $m_1$ being independent from the disease duration $d$. For some chronic diseases, this is not the case. An example is type 2 diabetes: after physiological onset, most patients do not have any symptoms and the disease remains undetected. After onset of clinical symptoms, the mortality already $m_1$ is higher compared to the mortality $m_0$ of a healthy person with the same age (and sex). Then, the therapy starts. During therapy, the mortality decreases and after some time with the disease the mortality increases again due to late sequelae. In the Danish diabetes register the J-shaped mortality ratio (i.e., $\frac{m_1}{m_0}$) is empirically evident [5]. There are other chronic diseases with duration being an important factor for mortality, for example, dementia [10] and systemic lupus erythematosus [1]. It is likely that duration is an important covariate for many of chronic diseases.

The aim of this article is the derivation of a partial differential equation (PDE) similar to Equation (1) in case the mortality rate $m_1$ depends on the
duration \(d\). Thus, this work is a generalization of the the previous articles [2, 4].

2 Basic equations for the illness-death model

As in [4] let \(S(t, a)\) and \(C(t, a)\) denote the numbers of healthy and diseased persons aged \(a\) at time \(t\). Based on the possible transitions from the Normal state in Figure 1 we get the following Cauchy problem for \(S(t, a)\):

\[
(\partial_t + \partial_a) S(t, a) = -(m_0(t, a) + i(t, a)) S(t, a)
\]

\[
S(t-a, 0) = S_0(t-a).
\]

Here \(S_0(t-a) = S(t-a, 0)\) is the number of healthy newborns at calendar time \(t-a\). Henceforth, the notation \(\partial_x\) means the partial derivative for the variable \(x\), \(x \in \{t, a, d\}\). The rates \(i, m_0\) and \(m_1\) in Figure 1 are assumed to be sufficiently smooth, such that the common uniqueness and existence theorems hold [9]. The unique solution \(S(t, a)\) is

\[
S(t, a) = S_0(t-a) \exp \left( -\int_0^a m_0(t-a + \tau) + i(t-a + \tau) d\tau \right).
\]

In case of the diseased persons, we have to distinguish between different disease durations. Let \(C^*(t, a, d)\) be the number of diseased persons aged \(a\) at time \(t\) having the disease for the exact duration \(d\), \(d < a\). For \(C^*(t, a, d)\) we also have a PDE:

\[
(\partial_t + \partial_a + \partial_d) C^*(t, a, d) = -C^*(t, a, d) m_1(t, a, d).
\]

The initial condition for making Equation 4 a Cauchy problem stems from the assumption that newly diseased persons may only enter from the Normal state. This means: \(C^*(t, a, 0) = i(t, a) S(t, a)\) for all \(t, a\). The unique solution of the Cauchy problem for \(C^*(t, a, d)\) is:

\[
C^*(t, a, d) = C^*(t-d, a-d, 0) \exp \left( -\int_0^d m_1(t-d + \tau, a-d + \tau) d\tau \right)
\]

\[
= i(t-d, a-d) S(t-d, a-d) e^{-\int_0^d m_1(t-d+\tau, a-d+\tau) d\tau}.
\]
The total number $C(t,a)$ of diseased persons can be obtained by integration:

\[
C(t,a) = \int_0^a C^*(t,a,\delta) \, d\delta \\
= \int_0^a i(t-\delta, a-\delta) S(t-\delta, a-\delta) e^{-\int_0^\delta m_1(t-\delta+\tau, a-\delta+\tau, \tau) \, d\tau} \, d\delta
\]

(5)

Summing up the previous equations, we get the following result for the age-specific prevalence. The result was given without derivation in [8].

**Theorem 1.** For the age-specific prevalence

\[
p(t,a) = \frac{C(t,a)}{S(t,a)+C(t,a)}
\]

it holds

\[
p(t,a) = \frac{\int_0^a i(t-\delta, a-\delta) \mathcal{M}_{t,a}(a-\delta) e^{-M_1(t,a,\delta)} \, d\delta}{\mathcal{M}_{t,a}(a) + \int_0^a i(t-\delta, a-\delta) \mathcal{M}_{t,a}(a-\delta) e^{-M_1(t,a,\delta)} \, d\delta},
\]

where

\[
\mathcal{M}_{t,a}(y) := \exp \left( - \int_0^y m_0(t-a+\tau, \tau) + i(t-a+\tau, \tau) \, d\tau \right)
\]

and

\[
M_1(t,a,d) := \int_0^d m_1(t-d+\tau, a-d+\tau, \tau) \, d\tau.
\]

As mentioned above, Equation (6) allows the calculation of the age-specific prevalence if the rates $i(t,a), m_0(t,a)$ and $m_1(t,a,d)$ are known.

As an observation we get:

**Remark 1.** $p$ does not depend on the number of newborns $S_0$.

To conclude this section, we list the assumptions that have been used to deduce Equation (6):

1. We consider a chronic (i.e., irreversible) disease. This means, there is no transition from the Disease to the Normal state.
2. The transitions are described by the rates $i, m_0$ and $m_1$. The rates are sufficiently smooth.

3. Newborns are disease-free.

4. Except for disease-free newborns, no one enters the population.

5. The only way out of the population is the Death state.

3 Differential equations for the age-specific prevalence

An enormous drawback of Equation (6) lies in the fact that it cannot be solved for the incidence $i$ even if the mortality rates $m_0$ and $m_1$ are known. If the duration $d$ does not play a role, it can be shown that $p$ fulfills a simple differential equation of the form (1) [2, 4]. In case of independence from $d$, we can also release some of the assumptions given at the end of the previous section (see [4] for details).

In this section, it is shown that with the assumptions recapped above, the age-specific prevalence $p$ fulfills a PDE similar to Equation (1). For this, define the mortality rate $m_1^\star$ by:

\[(7)\]
\[
m_1^\star(t, a) := \frac{\int_0^a m_1(t, a, \delta) C^\star(t, a, \delta)d\delta}{\int_0^a C^\star(t, a, \delta)d\delta}.
\]

Obviously, this definition needs the assumption that $\int_0^a C^\star(t, a, \delta)d\delta(= C(t, a)) \neq 0$ for $(t, a)$. At points $(t, a)$ such that $C(t, a) = 0$ define $m_1^\star(t, a) := 0$.

Since the numerator in Equation (7) is the total number of “incident” death cases among all diseased persons aged $a$ at $t$, the rate $m_1^\star(t, a)$ is the overall mortality rate of the diseased persons.

Assumed that $C$ fulfilled the PDE

\[(8)\]
\[
(\partial_t + \partial_a) C(t, a) = -m_1^\star(t, a) C(t, a) + i(t, a) S(t, a),
\]

then for $p = \frac{C}{S + C}$ it would hold

\[(9)\]
\[
(\partial_t + \partial_a) p = (1 - p) \left( i - p (m_1^\star - m_0) \right).
\]

\[1\] In stochastic contexts, what here is called rate is synonymously denoted as density.
Proof. Let $\partial := \partial_t + \partial_a$. Application of the quotient rule to $p = \frac{C}{S+C}$ yields $\partial p = \frac{(1-p)\partial C - p\partial S}{S+C}$. Inserting Equations (2) and (8) into the nominator of this expression yields Equation (9).

It remains open to prove Equation (8). With $\partial = \partial_t + \partial_a$ it holds:

\[
\partial C(t, a) = \partial \int_0^a C^*(t, a, \delta) \, d\delta
\]

\[
= \int_0^a \partial C^*(t, a, \delta) \, d\delta + C^*(t, a, a)
\]

\[
= \int_0^a (\partial_t + \partial_a + \partial_d)C^*(t, a, \delta) \, d\delta - \int_0^a \partial_d C^*(t, a, \delta) \, d\delta + C^*(t, a, a)
\]

\[
= - \int_0^a m_1(t, a, \delta) C^*(t, a, \delta) \, d\delta - \int_0^a \partial_d C^*(t, a, \delta) \, d\delta + C^*(t, a, a)
\]

\[
= -m_1^*(t, a) C(t, a) - (C^*(t, a, a) - C^*(t, a, 0)) + C^*(t, a, a)
\]

\[
= -m_1^*(t, a) C(t, a) + i(t, a) S(t, a).
\]

For the second equality, Leibniz’s integral rule (also known as differentiation under the integral sign) has been used.

In summary, we get:

\[
(\partial_t + \partial_a) p = (1 - p) \left( i - p (m_1^* - m_0) \right).
\]

Remark 2. If $m_1$ does not depend on the duration $d$, it holds $m_1^*(t, a, \delta) = m_1^*(t, a) = m_1(t, a)$. In this case, Equation (9) is equal to the PDE $(\partial_t + \partial_a) p = (1 - p) \left( i - p (m_1^* - m_0) \right)$ as in [4].

4 About the overall mortality $m_1^*$ of the diseased

In this section, the overall mortality $m_1^*$ of the diseased is examined further and illustrated by a numerical example.

For $C(t, a) > 0$ it holds

\[
m_1^*(t, a) = \int_0^a m_1(t, a, \delta) \frac{C^*(t, a, \delta)}{C(t, a)} \, d\delta.
\]
The fraction $C^{∗}(t,a,δ)/C(t,a)$ is the duration distribution of the diseased persons at $(t,a)$. Thus, $m^{∗}_{1}(t,a)$ depends on the duration distribution of the disease.

In addition, by inserting the expressions for $C^{∗}(t,a,d)$ into Equation (7) and cancelling out $S_{0}(t - a)$ one obtains

$$m^{∗}_{1}(t,a) = \frac{\int_{0}^{a} m_{1}(t,a,δ) i(t - δ, a - δ) M_{t,a}(a - δ) e^{-M_{t,a}(a - δ)} dδ}{\int_{0}^{a} i(t - δ, a - δ) M_{t,a}(a - δ) e^{-M_{t,a}(a - δ)} dδ}. \tag{10}$$

Hence, the overall mortality rate of the diseased depends on the age-specific incidence rate $i$. To be more specific, Equation (10) shows that at the point $(t,a)$, the incidence $i$ at all the previous points in time $(t - δ, a - δ)$, $δ \in [0,a]$, contributes to $m^{∗}_{1}(t,a)$. The dependence of $m^{∗}_{1}(t,a)$ on the past incidence $i(t - δ, a - δ)$, $δ \in [0,a]$, is not surprising. Consider two chronic diseases with onset at ages $a_{ℓ}$, $ℓ = 1, 2$, i.e., $i_{ℓ}(t,a) = 0$ for all $(t,a)$ where $a \leq a_{ℓ}$. If, say, disease 1 has a later onset than disease 2, $a_{1} > a_{2}$, then by definition it holds $m^{∗}_{1,i_{1}}(t,a') = 0$ for all $a' \in [a_{2},a_{1})$, whereas $m^{∗}_{1,i_{2}}(t,a')$ may be greater than 0.

To illustrate the dependency of $m^{∗}_{1}$ on the incidence we set up an example. We assume two hypothetical chronic diseases in a fictional population. Henceforth, we assume that $t,a$ and $d$ are measured in years $t,a,d \geq 0$.

For the mortality rate $m_{0}$ of the normal population we assume the Strehler-Mildvan form $m_{0}(t,a) = \exp(-11 - 0.04t + 0.1a)$. This is an approximation for the general mortality in the male German population as used by the official population projection of the Federal Statistical Office [6]. The calendar time $t$ is measured in years since 2010.

For the incidence of the first disease, we assume $i_{1}(t,a) = i_{1}(a) = \frac{(a-30)+}{2000}$, where $x_{+}$ means $x_{+} = \max(0,x)$. The incidence of the second disease is just $i_{2} = 0.1 i_{1}$.

In addition, let the mortality $m_{1}$ be given by $m_{1}(t,a,d) = R(d) m_{0}(t,a)$, where $R(d) = (0.2 d - 1)^{2} + 1$.

Figure 2 shows the overall mortality $m^{∗}_{1,i_{ℓ}}(t,a)$ in year $t = 1$ for the different incidences $i_{ℓ}$, $ℓ = 1, 2$, over the age $a$. The values have been calculated by Equation (10) using Romberg’s rule for integration. For ages below 50 the values $m^{∗}_{1,i_{1}}(t,a)$ rather agree, but diverge for ages between 50 and 80. For higher ages, the difference between $m^{∗}_{1,i_{1}}$ and $m^{∗}_{1,i_{2}}$ decreases again.

The reason for the differences can be seen in Figure 3 which depicts the duration distribution of the diseased persons $C(t = 1,a)$ for ages $a = 55,75,95$. 

\[7\]
Figure 2: Logarithm of the overall mortality of the diseased for two different incidence rates.

From Figures 2 and 3 it becomes apparent that, although $m_1(t, a, d)$ are the same for both diseases, the overall mortality $m_1^\star$ depends on the duration distribution of the diseased persons, which in turn depends on the incidence.

5 Discussion

This work generalizes the results of the previous articles [2] and [4] for the illness-death model as shown in Figure 1. In contrast to the previous articles, we do not need the assumption that the mortality of the diseased persons is independent from the duration of the disease. The modification that arises from possible duration dependence is the introduction of a measure for the mortality of the diseased persons, the overall mortality $m_1^\star$. We have shown that $m_1^\star$ depends on the duration distribution of the diseased persons, which
in turn is a consequence of the incidence rate. With respect to the aim of deriving the age-specific incidence from prevalence data, this seems to be a drawback. However, if the duration distribution of the diseased persons is known, then the calculation of \( m_1^* \) does not impose a problem. The request for having knowledge about the duration distribution is not unusual. It arises from the fundamental demand of epidemiology that the sample population (in a survey) should be a representative subset of the target population. Given that the duration distribution is known, calculation of \( m_1^* \) from the duration dependent mortality \( m_1 \) is possible. Another way of obtaining \( m_1^* \) is surveying it directly in an epidemiological study. If the sample population is representative for the target population – this means also representative with respect to the duration distribution – \( m_1^* \) may be obtained from standard survival analysis if the duration dependency is ignored. In this way, the overall mortality \( m_1^* \) is an easily accessible epidemiological measure.

If, furthermore, the mortality \( m_0 \) of the healthy, or at least the general mortality \( m = p m_1^* + (1 - p) m_0 \) is known, then Equation (9) can be used to obtain the incidence rate \( i \).

References

[1] Bernatsky S, Boivin JF, Joseph L et al (2006). Mortality in systemic lupus erythematosus. Arthritis Rheum 54(8): 2550-7.

[2] Brinks R (2011). A new method for deriving incidence rates from prevalence data and its application to dementia in Germany. [arXiv:1112.2720](arXiv:1112.2720)

[3] Brinks R (2012). On characteristics of an ordinary differential equation and a related inverse problem in epidemiology. [arXiv:1208.5476](arXiv:1208.5476)
[4] Brinks R (2012). On the age-, time- and migration dependent dynamics of diseases. arXiv:1209.1371

[5] Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K (2008). The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia 51 (12):2187-96.

[6] Federal Statistical Office of Germany (2009). 12. Population Projection [12. Koordinierte Bevölkerungsvorausberechnung] http://www.destatis.de, last access August 29th, 2013

[7] Hens N, Aerts M, Faes C et al (2010). Seventy-five years of estimating the force of infection from current status data. Epidemiol Infect 138(6):802-12.

[8] Keiding N (1991). Age-specific incidence and prevalence: a statistical perspective. J Royal Stat Soc A 154:371-412.

[9] Polyanin AD, Zaitsev VF, Moussiaux A (2000). Handbook of first order partial differential equations, Taylor & Francis, London

[10] Rait G, Walters K, Bottomly C et al (2010). Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 341:c3584.