

On the age-, time- and migration dependent dynamics of diseases

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This paper generalizes a previously published differential equation that describes the relation between the age-specific incidence, remission, and mortality of a disease with its prevalence. The underlying model is a simple compartment model with three states (illness-death model). In contrast to the former work, migration- and calendar time-effects are included. As an application of the theoretical findings, a hypothetical example of an irreversible disease is treated.

Keywords: Incidence; Remission; Mortality; Prevalence; Illness-Death Model; Compartment model; Epidemiology.

1 Introduction

With a view to basic epidemiological parameters such as incidence, prevalence and mortality of a disease, it has been proven useful to consider simple illness-death models [8] as shown in Figure 1. Depending on the context, sometimes these are referred to as state models or compartment models. Here we consider three states: Normal or non-diseased with number of people denoted as S (susceptible), the diseased state with number C (cases) and the death state.

The transition intensities between the states henceforth are denoted with the symbols as in Figure 1: incidence i , remission r and mortality rates¹ m_0 and m_1 . In general, the intensities depend on calendar time t , age a and sometimes also on the duration d of the disease.

¹The expressions *rate* and *density* are synonymously used in this article.

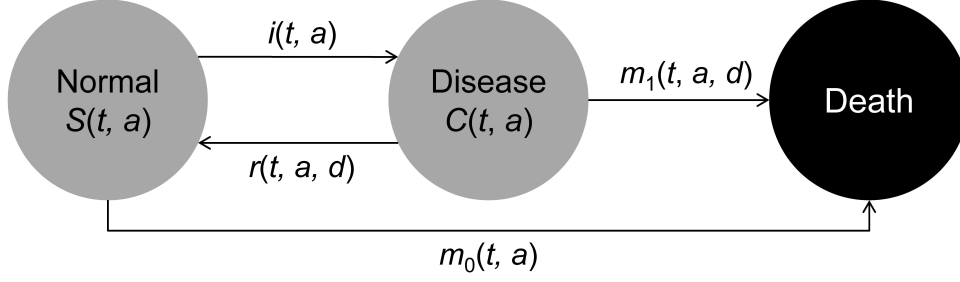


Figure 1: Simple illness-death model

Models of this kind are quite common, see for example [8], [9] or the text book [7]. Murray and Lopez ([13] and [14]) have considered such a compartment model with rates being independent from calendar time t and duration d . In the context of the *Global Burden of Disease* study of the *World Health Organization* they used following system of ordinary differential equations (ODEs) to describe the transitions between the three states:

$$\begin{aligned} \frac{dS}{da} &= -(i + m_0) \cdot S + r \cdot C \\ \frac{dC}{da} &= i \cdot S - (m_1 + r) \cdot C. \end{aligned} \tag{1}$$

By this system the changes in the numbers of the non-diseased and diseased persons aged a are related to the intensities as in Figure 1. Age plays here the role of temporal progression. This homogeneous linear system of ODEs looks relatively harmless, but is limited due to its heavy assumptions. By an easy calculation it can be shown that Eq. (1) implies the population being stationary. Let $N(a) := S(a) + C(a)$ denote the total number of persons alive in the population aged a . For $a \in [0, \omega]$ with $N(a) > 0$ define the age-specific prevalence

$$p(a) := \frac{C(a)}{C(a) + S(a)}. \tag{2}$$

Then from Eq. (1) it follows

$$\begin{aligned} \frac{dN}{da} &= \frac{dS}{da} + \frac{dC}{da} \\ &= -m_0 \cdot S - m_1 \cdot C \\ &= -N \cdot [(1 - p) \cdot m_0 + p \cdot m_1]. \end{aligned}$$

The term $(1 - p) \cdot m_0 + p \cdot m_1$ is the overall mortality m in the population. Hence, it holds $\frac{dN}{da} = -m \cdot N$, which is the defining equation of a stationary population, [16]. Although the model of a stationary population is widely used in demography, real populations merely are stationary. Moreover, the inclusion of the values S and C is disturbing. It would be better if Eq. (1) could be expressed in terms of the age-specific prevalence

(2), what indeed can be achieved. In [1] it has been shown, that system (1) can be transformed into the following one-dimensional ODE of Riccati type:

$$\frac{dp}{da} = (1 - p) \cdot (i - p \cdot (m_1 - m_0)) - r \cdot p. \quad (3)$$

The importance of Eq. (1) and (3) is obvious. For given incidence-, remission- and mortality-rates plus an initial condition, the age profile of the numbers of patients and the prevalence is uniquely determined, respectively. To state it clearly, the “forces” incidence, remission and mortality uniquely prescribe the prevalence - not only qualitatively but in these quantitative terms. This is called the *forward problem*: we infer from the causes – the forces – to the effect – the numbers of diseased or the prevalence, respectively. If in the scalar Riccati ODE (3) the age-profiles of the prevalence, mortality and remission are known, one can directly solve Eq. (3) for the incidence. This is the *inverse problem* – we conclude from the effect to the cause. This allows, for example, cross-sectional studies being used for incidence estimates, where otherwise lengthy follow-up studies are needed. For an example on real data, see [1]. Recently, it has been proven that the inverse problem is ill-posed [2].

The article is organized as follows: In the next section Eq. (3) is generalized allowing dependency on calendar time and migration. The central result is a partial differential equation (PDE). Similar to the ODE, in the general case there is a forward and an inverse problem for the PDE, too. These are analyzed in a simulated register data of a hypothetical chronic disease in the section thereafter. Finally, the results are summed up.

2 General equation of disease dynamics

In this section the simple illness-death model of Figure 1 is generalized. The rates i, r, m_0 and m_1 henceforth depend on age a and calendar time t , but are assumed to be independent from the duration d . Furthermore, let the numbers of the non-diseased $S(t, a)$ and diseased persons $C(t, a)$ aged a at time t be non-negative and partially differentiable. Define $N(t, a) := S(t, a) + C(t, a)$. Additionally, let $\sigma(t, a)$ and $\gamma(t, a)$ denote those proportions of $N(t, a)$, such that $\sigma(t, a) \cdot N(t, a)$ and $\gamma(t, a) \cdot N(t, a)$ are the net migration rates of non-diseased and diseased persons aged a at time t , respectively:

$$\begin{aligned} \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) S &= \sigma \cdot N - (i + m_0) \cdot S + r \cdot C \\ \left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) C &= \gamma \cdot N + i \cdot S - (m_1 + r) \cdot C. \end{aligned} \quad (4)$$

After introducing the age-specific prevalence $p(t, a)$ in year t ,

$$p(t, a) := \frac{C(t, a)}{C(t, a) + S(t, a)},$$

for $(t, a) \in D := \{(t, a) \in [0, \infty)^2 \mid C(t, a) \geq 0, S(t, a) \geq 0, C(t, a) + S(t, a) > 0\}$ the system (4) can be transformed into an equation similar to (3):

Theorem 2.1. *Let $S(t, a)$ and $C(t, a)$ be given by Eq. (4), then $p(t, a)$ is partially differentiable in D and it holds*

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t} \right) p = (1 - p) [i - p(m_1 - m_0)] - rp + \mu, \quad (5)$$

where $\mu := \gamma(1 - p) - p\sigma$ describes the impact of migration.

Proof. Follows from applying the quotient rule to $p(t, a) = \frac{C(t, a)}{C(t, a) + S(t, a)}$ and using (4). \square

Obviously, if the incidence- and mortality rates do not depend on the calendar time t , then from Eq. (5) with $\mu \equiv 0$ it follows (3). Hence, Eq. (3) does not depend on the stationary population assumption.

For applications in epidemiology it is important that solutions of Eq. (5) are *meaningful*, i.e. $p(t, a) \in [0, 1]$ for all $(t, a) \in D$. Therefor we note:

Theorem 2.2. *For all $(t, a) \in D$ following statements are equivalent:*

- (1) $p(t, a) = \frac{C(t, a)}{S(t, a) + C(t, a)}$ is a solution of Eq. (5).
- (2) $S(t, a) = (1 - p(t, a)) \cdot N(t, a)$ and $C(t, a) = p(t, a) \cdot N(t, a)$ are solutions to Eq. (4).

Proof. This follows by inserting the expressions into the PDEs. \square

By Theorem 2.2 a solution $p(t, a)$ of Eq. (5) can be written as $p(t, a) = \frac{C(t, a)}{N(t, a)}$ with $N(t, a) = S(t, a) + C(t, a)$. For $(t, a) \in D$ this implies $p(t, a) \in [0, 1]$.

The migration term μ will be analyzed further now. Let $\varphi := \sigma + \gamma$ be the overall migration rate. We split all migration rates f , $f \in \{\varphi, \sigma, \gamma\}$ into a positive part $f_+ \geq 0$ (immigration) and a negative part $f_- \geq 0$ (emigration):

$$f = f_+ - f_-, \text{ for } f \in \{\varphi, \sigma, \gamma\}.$$

Moreover, for $\varphi_-(t, a) > 0$ define $p_-^{(m)}(t, a) := \frac{\gamma_-(t, a)}{\varphi_-(t, a)}$ the prevalence of the disease in the emigrants and for $\varphi_+(t, a) > 0$ define $p_+^{(m)}(t, a) := \frac{\gamma_+(t, a)}{\varphi_+(t, a)}$ the prevalence in the immigrants.

Proposition 2.1. *With the notations as above it holds*

$$\mu(t, a) = \begin{cases} \varphi_+(t, a) \cdot p_+^{(m)}(t, a) \\ -\varphi_-(t, a) \cdot p_-^{(m)}(t, a) - \varphi(t, a) \cdot p(t, a), & \text{for } \varphi_-(t, a), \varphi_+(t, a) > 0; \\ \varphi_+(t, a) \cdot \left[p_+^{(m)}(t, a) - p(t, a) \right], & \text{for } \varphi_-(t, a) = 0, \varphi_+(t, a) > 0; \\ -\varphi_-(t, a) \cdot \left[p_-^{(m)}(t, a) - p(t, a) \right], & \text{for } \varphi_-(t, a) > 0, \varphi_+(t, a) = 0; \\ 0, & \text{for } \varphi_-(t, a) = \varphi_+(t, a) = 0. \end{cases}$$

Proof. For all $(t, a) \in D$ it holds $\mu = \gamma - \varphi \cdot p$. By splitting this expression into positive and negative parts, the Proposition follows. \square

With the assumption that the prevalence of those aged a at time t who immigrate is the same of those who emigrate, say $p^{(m)}(t, a)$, then it holds

$$\mu = \varphi (p^{(m)} - p). \quad (6)$$

Hence, if the prevalence $p^{(m)}$ of the migrants is the same as of those who stay, $p^{(m)} \equiv p$, the change in prevalence $(\frac{\partial}{\partial a} + \frac{\partial}{\partial t})p$ does not depend on migration.

This is an important result, because in illness-death models the assumption of absence of migration is often made. In our framework this restriction is not necessary. Even if there is migration, but the prevalence in the migrants is the same as in the resident population, then the prevalence is not affected by migration.

The solution of Eq. (5) can be obtained by the methods of characteristics [15]. Let an initial condition of the form $p(a, 0) = p_0(a)$ be given, then we have a so called Cauchy problem, which has a unique solution if the right-hand side of the PDE is sufficiently smooth [15]. This solution is calculated as follows. Assume, the prevalence for those aged \tilde{a} in year \tilde{t} has to be calculated. First, rearrange $(\frac{\partial}{\partial t} + \frac{\partial}{\partial a})p$ such that

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t} \right) p = \alpha(t, a) + \beta(t, a) p + \gamma(t, a) p^2.$$

Second, solve the initial value problem given by following Riccati ODE:

$$\frac{dy(\tau)}{d\tau} = \alpha(\tau + a_0, \tau) + \beta(\tau + a_0, \tau) y + \gamma(\tau + a_0, \tau) y^2, \quad (7)$$

and initial value $y(0) = p_0(a_0)$ where $a_0 := \tilde{a} - \tilde{t}$. Then, an easy calculation shows that $y(\tilde{t}) = p(\tilde{t}, \tilde{a})$ is the desired value.

3 Application on a simulated register

In this section, the application of the above-formulated Cauchy problem on a simulated register of a chronic disease is shown. Since the disease is assumed to be irreversible, it holds $r \equiv 0$. First, we address a direct problem: From given age-specific prevalence in some point in time t_0 we want to deduce the age-specific prevalence in t_1 , $t_1 > t_0$, by applying Eq. (5) with $\mu \equiv 0$. Second, an inverse problem is formulated. Assume in the year t_0 the functions $p_0 = p(t_0, \cdot)$, $i(t_0, \cdot)$, $m_0(t_0, \cdot)$ and $m_1(t_0, \cdot)$ were measured. If in year t_1 , $t_1 > t_0$, the age profile of the prevalence $p(t_1, \cdot)$ is given, the question arises: how has the course of the age-specific incidence changed in the meantime? This is an inverse problem, because we infer from the effect (prevalence in t_1) on the causes. Here we will formulate a simple, straight forward solution by an optimization approach.

Both problems will be treated based on data of a simulated register. The register is designed such that in a period of 150 years all persons are tracked from birth to death.

For each person, the date of an eventual diagnosis of the chronic disease is recorded. For the simulation, the following assumptions are placed as a basis:

1. In each calendar year 0 to 150 2,000 people are born. The births during the calendar year follow a uniform distribution.
2. The mortality of the non-diseased persons is of Strehler-Mildvan type and is given by the equation

$$m_0(t, a) = \exp(-10.7 + 0.1a) \cdot (1 - 0.002)^{(t-20)_+}.$$

The notation $(t - 20)_+$ denotes the positive component of the expression $(t - 20)$. The exponential term approximates the current mortality of men in Germany, the second factor takes the increasing life expectancy into account.

3. The incidence is described by the equation

$$i(t, a) = \frac{(a - 30)_+}{3000} \cdot 0.99^{(t-50)_+}. \quad (8)$$

4. The relative risk of death is constant for all ages and times:

$$R(t, a) = \frac{m_1(t, a)}{m_0(t, a)} = 2.$$

After the simulation, each person in the register is represented by four pieces of information:

- 1) A unique identification number (an integer),
- 2) Calendar year of birth,
- 3) The person's age in years at diagnosis (0 if the person does not fall ill),
- 4) Age of death of the person in years.

Entries 2) - 4) in the register are given to three decimals, which corresponds to a precision of one day. The identification number of the person is an ongoing counter. The date of birth (in calendar years) is given by the simulated year, the decimals are drawn from a uniform distribution $[0, 1)$. To decide if a thus far non-diseased person born in year τ becomes ill or dies without the disease, a competing risk approach in a discrete event simulation (DES) is accomplished. Based on the cumulative distribution function of the common risk (total intensity $i(\tau + a, a) + m_0(\tau + a, a)$), the age a_0 of event is drawn by the inverse transform sampling (inversion method, [5]). Based on a comparison between $i(\tau + a_0, a_0)$ and $m_0(\tau + a_0, a_0)$, it is decided whether the onset of the disease or the death without disease occurred. In the first case a_0 represents the

age at disease's onset, in the second case, a_0 is the age of death. If the person gets the disease, the age of death is simulated (conditional on reaching the age a_0).

As in the calendar years 0 to 150 exactly 2000 people are born every year, the hypothetical register contains $151 \cdot 2000 = 302,000$ persons. Then, the events of the hypothetical register are transformed into a Lexis diagram of five years intervals [10]. This allows an easy extraction of the person-years and the numbers of events in the corresponding age- and period classes.

In both test cases, in the direct and the inverse problem, we assume information to be given only in two points in time, t_0 and t_1 . Of course, three or more points in time would be advantageous, but with respect to applicability in epidemiological contexts, the test problems try to mimic a minimalistic setting.

3.1 Direct problem

Assume we have measured the age profile $p_0 = p(t_0, \cdot)$ of the prevalence in t_0 , and the age-specific incidence $i(t_0, \cdot)$ and mortality densities $m_0(t_0, \cdot)$ and $m_1(t_0, \cdot)$. Furthermore, at a later point in time $t_1 > t_0$ let the age-specific rates $i(t_1, \cdot)$ and mortalities $m_0(t_1, \cdot)$ and $m_1(t_1, \cdot)$ be given. The direct problem refers to the question: what can be said about the age-specific prevalence $p(t_1, \cdot)$ in t_1 ?

To answer this question, age-specific incidence and mortality rates at two time points $t_0 = 120$ and $t_1 = 140$ (years) are extracted from the register. In addition, the age-specific prevalence $p(t_0, \cdot)$ is collected at t_0 . Figure 2 shows the extracted age-specific incidence density (dashed lines) in t_0 (red) and t_1 (blue) in comparison with the theoretical values (solid lines).

Now consider the Cauchy problem that is given by Eq. (5) with the initial condition $p(t_0, \cdot) = p_0$. For the solution one needs the functions $i(t, \cdot)$, $m_0(t, \cdot)$ and $m_1(t, \cdot)$ for all time points t between t_0 and t_1 . For this, the function values are interpolated affine-linearly. The initial value problem Eq. (7) is solved numerically using the MATLAB² function `ode45`.

If we compare the numerical solution of the Cauchy problem in year $t_1 = 140$ with the actually observed prevalence in the year 140, one gets the result as shown in Figure 3.

Visually this gives a fairly good agreement between the predicted curve with the actually observed age-specific prevalence. The maximum absolute deviation is 0.0146, which means that in this example the prevalence can be predicted up to 1.5 percent points. The largest deviation is in the oldest age class, when we have only a few cases of the disease.

3.2 Inverse problem

In epidemiological studies, it is more laborious to measure incidence rates than prevalences. Hence, in practice, the following inverse problem is much more important than

²The MathWorks, Natick, Massachusetts, USA

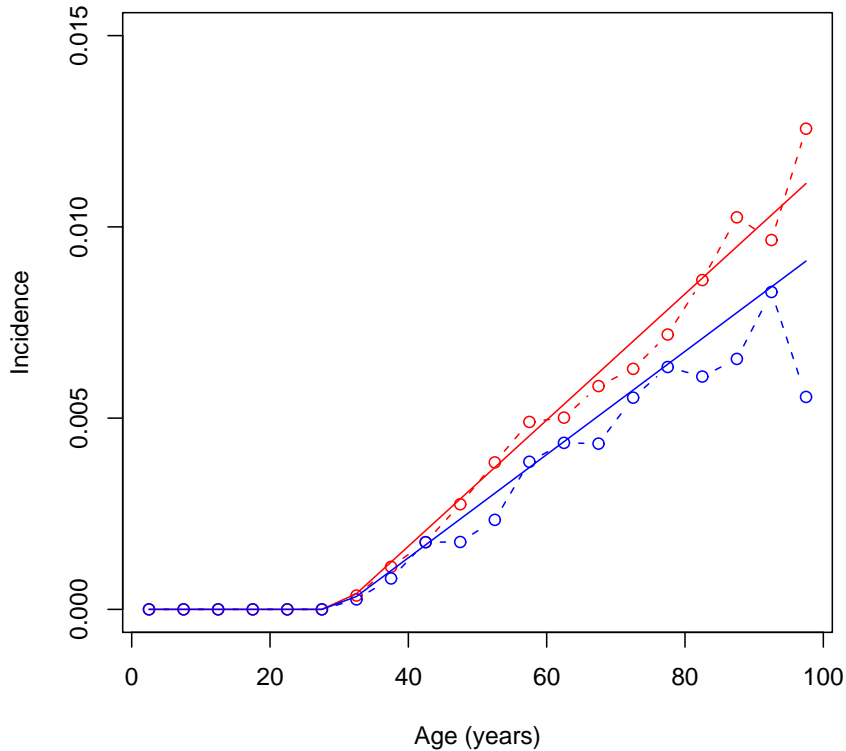


Figure 2: Age-specific incidence density extracted from the register (dashed lines) at $t_0 = 120$ (red) and $t_1 = 140$ (blue) in comparison with the theoretical values (solid lines).

the direct problem of the previous section. Assume in the year $t_0 = 120$ the functions $p_0 = p(t_0, \cdot)$, $i(t_0, \cdot)$, $m_0(t_0, \cdot)$ and $m_1(t_0, \cdot)$ are known. Moreover, in year $t_1 = 140$ let the age profile of the prevalence $p(t_1, \cdot)$ be given. The functions $m_0(t_1, \cdot)$ and $m_1(t_1, \cdot)$ are also assumed to be known (for example from other epidemiological studies). The question then is, how well the incidence $i(t_1, \cdot)$ in the year t_1 can be derived from this information. For simplicity, we assume that the incidence of $i(t_1, \cdot)$ in t_1 can be expressed as a product

$$i(t_1, \cdot) = i(t_0, \cdot) \cdot (1 - h), \quad (9)$$

where $h \in [0, 1]$. The upper limit for h stems from the fact, that incidence rates are non-negative. The lower limit reflects the prior knowledge, that incidence has not increased in t_1 compared to t_0 : $i(t_1, a) \leq i(t_0, a)$, for all $a \in [0, \infty)$. Equation (9) corresponds to a proportional hazards approach, which is used widely in epidemiology.

To solve this inverse problem, we formulate an optimization problem. For given $h \in [0, 1]$ and $i(t_0, \cdot)$ by Eq. (9) the function $i(t_1, \cdot)$ is defined. If furthermore $p(t_0, \cdot)$,

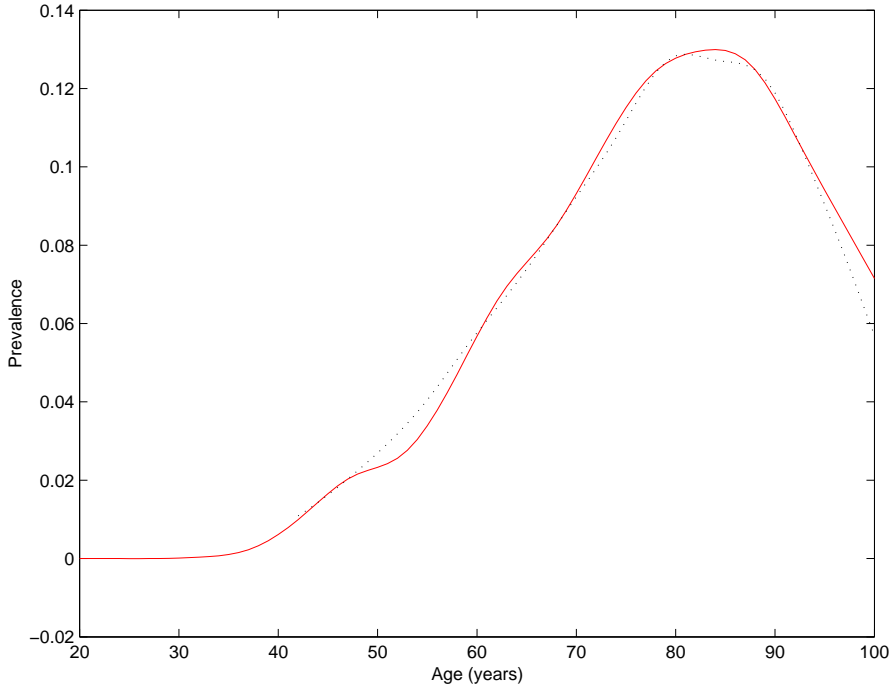


Figure 3: Numerical solution of the direct problem (dashed line) compared to the observed prevalence in year $t_1 = 140$ (solid line).

$m_0(t_0, \cdot)$, $m_0(t_1, \cdot)$, $m_1(t_0, \cdot)$ and $m_1(t_1, \cdot)$ are known, then we are in the situation to calculate a unique function $\hat{p}_h(t_1, \cdot)$ by solving the Cauchy problem described in the previous subsection 3.1. The solution $\hat{p}_h(t_1, \cdot)$ of the direct problem depends on h . We can compare $\hat{p}_h(t_1, \cdot)$ with the measured prevalence $p(t_1, \cdot)$ in the register. Thus, we seek for $h^* \in [0, 1]$ that minimizes the Euclidean distance between $\hat{p}_h(t_1, \cdot)$ and $p(t_1, \cdot)$:

$$h^* = \arg \min_{h \in (0,1)} \int_{A_{t_1}} |\hat{p}_h(t_1, a) - p(t_1, a)|^2 da, \quad (10)$$

where $A_{t_1} = \{a \in [0, \infty) \mid (t_1, a) \in D\}$.

Figure 4 shows the Euclidean distance between the prevalence $p(t_1, \cdot)$ in the register and the solution $\hat{p}_h(t_1, \cdot)$ as a function of h .

From the graph in Figure 4 it is obvious that the square of the distance is minimized at about $h^* = 0.25$. Since from the 50th calendar year the incidence decreases by 1% per year and a period of 20 years was considered, a factor $1 - h$ of about $0.99^{20} = 0.82 = (1 - 0.18)$ is expected. The revealed value $h^* = 0.25$ is about a factor of 1.4 too large.

4 Discussion

In this work we developed a new equation linking incidence-, remission- and mortality-rates with prevalence of a disease. In contrast to former works, the assumptions of

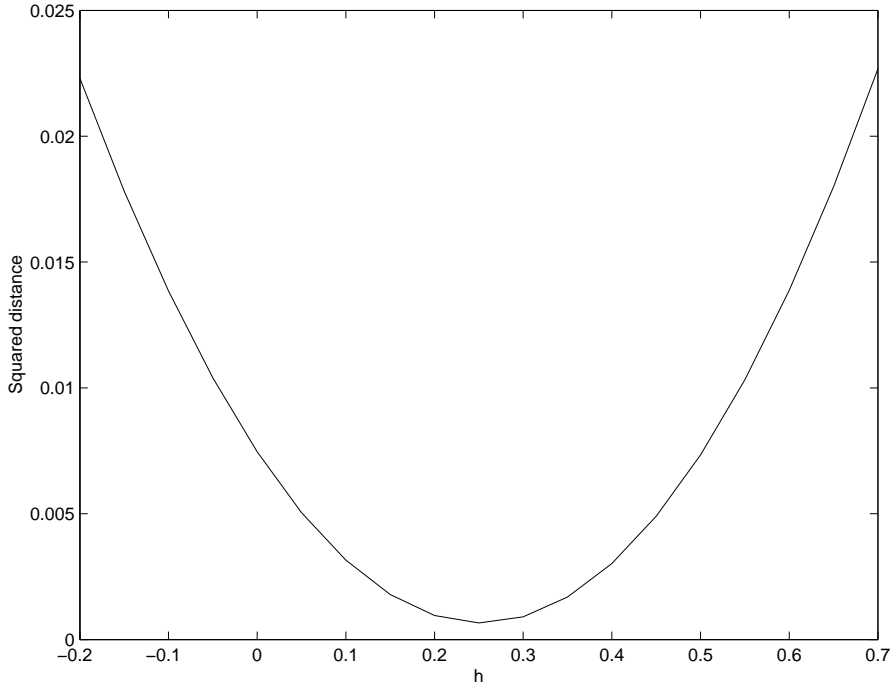


Figure 4: Euclidean distance (as in Eq. (10)) as a function of h . There is a unique minimum $h^* = 0.25$.

stationary populations, independence from calendar time and zero net migration have been released. The new equation has a wide range of applicability in epidemiological, health care and health economic contexts.

However, it has several limitations. First, Eq. (5) needs the remission rate r and mortality rate m_1 of the diseased to be independent from the duration d of the disease. In real diseases independence from duration is only an approximation. For many infectious diseases, immune response is dependent on the time since onset of the disease. Also in chronic diseases duration since onset plays a major role. For example, the age- and sex-adjusted mortality due to coronary heart disease roughly doubles for each 10-year increase in diabetes duration. The all-cause mortality increases by a factor of 1.2 per 10-year duration, [4].

Second, although the new equation is not limited to the case $\mu \equiv 0$, in practical applications information about the health of immigrants *and* emigrants is seldom obtainable. By Proposition 2.1 reasonable knowledge of prevalence in all migrants is necessary to accurately treat the case $\mu \neq 0$. To give an example, countries with large-scale immigration programs such as Canada observe a so-called *healthy immigrant effect* with respect to chronic diseases: immigrants are healthier than residents, [11]. Assumed that the emigrants from Canada have the same prevalence as the residents, it would follow $\mu \neq 0$. However, surveys about the health status of emigrants are missing. The reason is obvious, Canada's taxpayer-funded health care system is interested in measuring health of those who immigrate, but not in those who emigrate. Hence, information is lacking

and assumptions have to be made.

Third, Eq. (5) only considers prevalence in migrants at the moment of emigration or immigration. Of course, large scale immigration is likely to change the incidence of the disease in the population, because immigrants' health adapts to the new environment. There are many examples where immigrants from the developing countries increase incidence of diabetes and related complications when adopting westernized lifestyle, [12]. The opposite may also be true, in Canada immigrants continue to have a lower relative risk of chronic conditions compared to the native-born, even many years after immigration, [11].

Beside theoretical considerations, we use the new equation in a simulated register of a hypothetical chronic disease. The register has been simulated by Monte Carlo techniques and has been analyzed by a numerical implementation of the new equation. To check the practical applicability of the analysis, the simulation and the analysis have been strictly separated, i.e. neither was the PDE used in simulating the register, nor was information other than explicitly mentioned, used as input for the simulation exploited in the analysis. The PDE has only been used in the analysis of the direct and inverse problem. In the direct problem, the prevalence at the later point in time t_1 could be predicted from the prevalence in t_0 twenty years earlier with a high accuracy. Of course, the obtained accuracy is a result of the structure inherent to the simulation. The solution of both, direct and inverse problem, uses an affine-linear interpolation for the incidence- and mortality rates between t_0 and t_1 . In the simulated register this works well, because it reflects the trends in the incidence and mortalities. Affine-linear interpolation will impose problems if the incidence trend turns around between t_0 and t_1 . An example for a change of trends can be found in [3]: from 1995 to 2004 incidence of diabetes is found to be rising with an average of 5.3% per year in all age classes, and from 2005 to 2007 incidence is declining with 3.1% per year.

In the inverse problem, the incidence in t_1 was reconstructed from the observed prevalence in t_1 . Provided that the right-hand side of Eq. (5) is sufficiently smooth, existence of $h^* \in [0, 1]$ follows from the continuous dependency of the solution of the Cauchy problem on h from the compact interval $[0, 1]$. Continuous dependency can be seen by noting that the solution constructed by the methods of characteristics inherits its smoothness properties from the smoothness of the right-hand side of Eq. (7), [6]. The question remains why the result (in terms of h^*) is about a factor 1.4 too large. The approach in solving the inverse problem is the proportional hazards assumption Eq. (9). Indeed, the simulation considers a decline of exponential type, see Eq. (8). Although the exponential in this case can be approximated by an affine-linear interpolation function quite well, it appears that the solution of the inverse problem reacts quite sensitively on inaccuracies. This is in line with our observation, that the inverse problem is ill-posed [2].

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