Abstract

Recently, we proposed an state model (compartment model) to describe the progression of a chronic disease with an pre-clinical ("undiagnosed") state before clinical diagnosis. It is an open question, if a sequence of cross-sectional studies with mortality follow-up is sufficient to estimate the true incidence rate of the disease, i.e. the incidence of the undiagnosed and diagnosed disease. In this note, we construct a counterexample and show that this cannot be achieved in general.

1 Introduction

1.1 Compartment model

Recently, we introduced a compartment model with a pre-clinical stage preceding the clinical stage. The model involves calendar time $t$, and the different ages $a$ of the subjects in the population. The transition rates between the states are denoted as in Figure.

Using the definition $N(t, a) = S(t, a) + U(t, a) + C(t, a)$ and setting

$$p_0(t, a) = \frac{S(t, a)}{N(t, a)}$$

$$p_1(t, a) = \frac{U(t, a)}{N(t, a)}$$

$$p_2(t, a) = \frac{C(t, a)}{N(t, a)}$$

the compartment model in Figure is governed by a system of partial differential equations (PDEs):
Figure 1: Chronic disease model with four states and the corresponding transition rates. People in the state *Normal* are healthy with respect to the disease under consideration. After onset of the disease, they change to state *Undiagnosed* and maybe later to the state *Diagnosed*. The absorbing state *Dead* can be reached from all other states. The numbers of persons in the states and the transition rates depend on calendar time $t$ and age $a$.

\[
\begin{align*}
(1) & \quad (\partial_t + \partial_a)p_1 = -(\lambda_0 + \lambda_1 + \mu_1 - \mu)p_1 - \lambda_0 p_2 + \lambda_0 \\
(2) & \quad (\partial_t + \partial_a)p_2 = \lambda_1 p_1 - (\mu_2 - \mu)p_2.
\end{align*}
\]

For brevity we have written $\partial_x = \frac{\partial}{\partial x}$, $x \in \{t, a\}$. In Eq. (1) – (2) the general mortality $\mu$ is given by

\[
(3) \quad \mu = p_0 \mu_0 + p_1 \mu_1 + p_2 \mu_2.
\]

Together with the initial conditions $p_1(t, 0) = p_2(t, 0) = 0$ for all $t$, the system (1) – (2) completely describes the temporal dynamics of the disease in the considered population. The quantity $p_0$ can be obtained by

\[
(4) \quad p_0 = 1 - p_1 - p_2.
\]

### 1.2 Direct and inverse problem

Assumed that the functions $\lambda_0, \lambda_1, \mu_1, \mu_2, \mu$ on the right-hand sides of system (1) – (2) are sufficiently smooth, then the associated initial value problem
\[ p_1(t, 0) = p_2(t, 0) = 0 \] for all \( t \) has a unique solution. This means that together with the initial condition, there is a function

\[ \Phi : \Theta = (\lambda_0, \lambda_1, \mu_1, \mu_2, \mu) \mapsto P = (p_1, p_2). \]

Given the initial conditions, the operator \( \Phi \) maps the transition rates \( \Theta \) onto the uniquely associated prevalence functions \( \Phi(\Theta) = P = (p_1, p_2) \). This problem is called the direct problem or forward problem \(^2\). Similar to the simpler compartment model in \(^3\), the question arises if and under which circumstances the opposite way is possible. Does a series prevalence studies \( P \) allow to estimate the transition rates \( \Theta \)? Mathematically, this problem is expressed as inversion of the function \( \Phi \). Given \( P \), the question is if there is a unique \( \Theta \) such that \( \Phi(\Theta) = P \)? The problem of estimating the rates from prevalence data, is called an inverse problem \(^2\). It is not guaranteed that the inverse problem has a solution. Examination of conditions such that the inverse problem has a solution is called the analysis of identifiability \(^4\).

Under certain circumstances, the operator \( \Phi \) is indeed invertible. Assumed that the mortality rates \( \mu_1, \mu_2 \), and \( \mu \) are known, then for given \( P = (p_1, p_2) \) the system \(^1\) – \(^2\) can be solved for \( \lambda_0 \) and \( \lambda_1 \). Thus, in these cases \( \Phi \) is invertible.

In the next section, we will show that is not always the case.

## 2 Identifiability problem

We consider two prevalence studies at calendar times \( t_1 < t_2 \) with mortality follow-up. This means, on the one hand we have estimates for the age courses of the prevalences \( p_1 \) and \( p_2 \) at \( t_1 \) and \( t_2 \). On the other hand, we have additional information if and when any participant at \( t_1 \) has died before \( t_2 \). Let us assume that for any participant who deceased between \( t_1 \) and \( t_2 \), we do not have information about what state the person was in at the time of death. For example, a person who was in the Normal state at \( t_1 \) and died before \( t_2 \) could have deceased when he was still in the Normal state, in the Undiagnosed state or in the Diagnosed state. An exception is someone dying between \( t_1 \) and \( t_2 \), who was in the Diagnosed state. As the Diagnosed state can only be left via the transition to Dead state, the information from the mortality follow-up helps to estimate \( \mu_2 \). Thus, the mortality follow-up contributes to estimate the general mortality \( \mu \) or occasionally the mortality \( \mu_2 \), but not to estimate \( \mu_0 \) or \( \mu_1 \).

The question arises: Given \( p_k(t_j, \cdot), j, k = 1, 2, \mu(t^*, \cdot) \) and \( \mu_2(t^*, \cdot) \) for some \( t^* \) with \( t_1 < t^* < t_2 \), are we able to estimate the rates \( \lambda_0, \lambda_1, \mu_0, \) and \( \mu_1 \) at
In the following we will show that this is not the case. This is done by constructing a counterexample with given \( p_1, p_2, \mu, \mu_2 \) but different \( \lambda_0, \lambda_1, \mu_0, \) and \( \mu_1. \)

Consider the system (1)–(2) being in equilibrium such that \( \partial_t p_k(t^*, a) = \partial_a p_k(t^*, a) = 0, \) \( k = 1, 2, \) for all \( a. \) Furthermore, let \( p_0 = 0.5, p_1 = 0.3 \) and \( p_2 = 0.2, \mu = 0.6, \mu_2 = 0.8. \) Obviously, it holds \( p_0 + p_1 + p_2 = 1. \) From \( \partial_x p_2 = 0, \) \( x \in \{t, a\} \) it follows that \( \lambda_1 = (\mu_2 - \mu)p_2/p_1 = \frac{4}{30}. \) If we choose \( \mu_1^{(1)} = 0.5 \) and \( \mu_1^{(2)} = 0.6, \) then from \( \mu = p_0\mu_0 + p_1\mu_1 + p_2\mu_2 \) it follows that \( \mu_0^{(1)} = 0.58 \) and \( \mu_0^{(2)} = 0.52. \) In addition, \( \partial_x p_1 = 0, \) \( x \in \{t, a\} \) implies \( \lambda_0 = (\lambda_1 + \mu_1 - \mu)p_2/p_1. \) Thus, it holds \( \lambda_0^{(1)} = 0.02 \) and \( \lambda_0^{(2)} = 0.08. \) The results are summarized in Table 1.

| Variable | Value 1 | Value 2 |
|----------|---------|---------|
| \( p_0 \) | 0.5     |         |
| \( p_1 \) |         | 0.3     |
| \( p_2 \) |         | 0.2     |
| \( \mu \) |         | 0.6     |
| \( \mu_2 \) |         | 0.8     |
| \( \lambda_1 \) | \( \frac{4}{30} \) |         |
| \( \mu_1 \) | 0.5     | 0.6     |
| \( \mu_0 \) | 0.58    | 0.52    |
| \( \lambda_0 \) | 0.02    | 0.08    |

Table 1: Example for non-identifiability of the system (1)–(4). In an equilibrium state \( (\partial_x p_k = 0, \) \( k = 1, 2, \) \( x \in \{t, a\}) \), measured values in the upper half of the table are consistent with the values in the lower half.

Hence, from given \( p_1, p_2, \mu, \mu_2, \) in equilibrium, we were able to construct different \( \lambda_0, \lambda_1, \mu_0, \) and \( \mu_1, \) which are consistent with the system (1)–(4). This implies that two cross-sections at \( t_1 \) and \( t_2 \) with mortality follow-up are not sufficient to make the system identifiable.

### 3 Conclusion

In this technical note it was shown by a counterexample that two cross-sectional studies with mortality follow-up are not sufficient to make the system (1)–(4) identifiable. This means, from two cross-sectional studies and measured \( p_k, \) \( k = 0, 1, 2, \) and known \( \mu, \mu_2 \) it is not possible to estimate the incidence rates \( \lambda_0 \) and \( \lambda_1. \)
The counterexample was constructed by the system \((1) - (2)\) being in equilibrium. This is not a loss of generalizability. It is sufficient to find one example of non-identifiability to prove non-existence of a solution of the inverse problem.

Note that from measured \(p_k, \ k = 0, 1, 2,\) and known \(\mu, \mu_2,\) the rate \(\lambda_1\) is estimable. This can be seen by solving Eq. \((2)\) for \(\lambda_1.\)

**References**

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