



# The epidemiological models of Karl-Peter Haderler

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Dedicated to the memory of my friend KP Haderler

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## ABSTRACT

The most frequently cited articles out of KP Haderler's 45 papers with epidemiological applications are summarized. Parasitic diseases which increase the death rate of the hosts proportional to the integer number of parasites present were described by integral equations for the generating function of the age- and time-dependent number of parasites. A model was derived for a population structured by the continuous level of parasitic infection. Stimulated by the spread of AIDS a new class of epidemic models was developed which take into account explicitly the formation and separation of pairs. For predator-prey populations with parasitic infections threshold conditions for the persistence of the predator were derived. The interaction of epidemics and demography was analysed. Several epidemiological conditions led to backward bifurcations associated with multiple infective stationary states.

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## 1. Introduction

Hillen, Lutscher, and Müller (2006) describe the wide range of topics covered in KP Haderler's mathematical and biological oeuvre. With eight papers and his last book (Haderler, 2017) on quiescent phases in dynamical systems since 2007 he even widened his field of interests (see e.g. Haderler, 2013). The two areas to which he contributed most are the dynamics of infectious diseases (including parasites) (45 papers) and eigenvalue problems (31 papers, see Thieme, 2017). Out of his 24 papers on reaction-diffusion processes, 12 articles are covered in the survey on hyperbolic and kinetic models for self-organized biological aggregations and movement by Eftimie (2012).

This brief and non-exhaustive summary of his epidemiological papers covers in five sections the following themes: parasitic diseases (Sect. 2), sexually transmitted infections (Sect. 3), predator-prey populations with parasitic infections (Sect. 4), demography and epidemics (Sect. 5) and epidemiological models with backward bifurcation (Sect. 6).

## 2. Models for the level of parasitic infection

From 1983 to 1986 KP Haderler published eleven papers on infections with a discrete level of parasitic infection. On three of them we collaborated. In Haderler and Dietz (1983) we started with the number of individuals of a given age at a certain time carrying an integer number of parasites. New parasites are acquired at a rate which is proportional to a function of the mean

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number of parasites per host. An individual host dies according to an age-dependent death rate plus an infection-induced death rate which is proportional to the number of parasites present. The parasites die within the host at a constant rate. If an individual dies, then all parasites in this individual die simultaneously. The population of hosts is described by an immigration-death-process. Individuals enter the population at age zero without parasites.

By introducing a generating function the infinite system of hyperbolic partial differential equations is reduced to an integral equation. A positive equilibrium exists if the contact rate exceeds a certain threshold value for which an explicit formula is derived. In the equilibrium the number of parasites per host of a given age has a Poisson distribution and the mean number of parasites per host increases asymptotically for large infection rates as the square root of the equilibrium infection rate. Since the mean number of parasites per host depends on the age of the host the distribution of parasites in the total population is a mixture of Poisson distributions and therefore it is overdispersed, i.e. the variance is larger than the mean.

This model was extended in [Hadeler and Dietz \(1984\)](#) to parasites which reproduce within their host.

[Hadeler \(1984a\)](#) also considered hosts with Lotka birth law, i.e. the number of newly added hosts is related to the total population size, where the number of parasites affects the per capita birth rate. He reduced the infinite system of equations to a system of two coupled integral equations for the acquisition rate of parasites and the number of newborn hosts. Accordingly, the host population shows exponential growth or decay with stationary age distribution and the acquisition rate is constant. He derived an explicit expression for the threshold contact rate which ensures a nontrivial endemic equilibrium.

If certain concavity conditions, how the transmission function depends on the mean parasite load of a host, are violated, then backward bifurcations and hysteresis effects may occur ([Hadeler, 1984b](#)). In [Hadeler \(1985\)](#) the transmission function and the birth rate of the hosts may depend on the total size of the host population.

[Anderson and May \(1978\)](#) reduced the system of infinitely many ordinary differential equations for the number of parasites in hosts with a constant death rate to a system of two differential equations by heuristically assuming a negative-binomial distribution for the number of parasites per host. They argued that this overdispersed distribution provides a good fit to the empirical data. Few hosts carry a very high load of parasites, while many hosts are without parasites at all or with only a small number. [Kretzschmar \(1993\)](#) presents a detailed comparison of the rigorous infinite dimensional system and the heuristic two-dimensional system. In her comparison she also investigates the effect of the parasite load on the birth rate, which was not included in the model of Anderson and May. She concludes that the overdispersion of the invariant parasite distribution is only reached for time tending to infinity whereas the underlying distribution of the two-dimensional model is always overdispersed with a fixed degree of overdispersion for all times. The advantage of the infinite dimensional model is the possibility to study the effect of individual model parameters on the degree of overdispersion.

[Hadeler \(1987\)](#) and [Waldstätter, Hadeler, and Greiner \(1988\)](#) divided the population into classes of noninfected and infected individuals. The level of infection is given by a real variable and modelled by a diffusion equation. With a novel approach the authors showed that the linear part of the model for a constant infection rate has a solution in some suitable Hilbert space. [Milner and Patton \(2003\)](#) adopt this model structure. They start with a model for a discrete number of parasites, take a diffusion limit and show good agreement of their new model with observations.

### 3. The role of pair formation in the dynamics of sexually transmitted infections

The emergence of the AIDS epidemic in the early 1980s stimulated the development of numerous mathematical models for the prediction of future AIDS cases and the evaluation of potential control interventions. [Dietz and Hadeler \(1988\)](#) proposed a new model for sexually transmitted diseases (STDs) which takes into account pair formation. If two susceptible individuals form a pair they are temporarily immune to infection as long as they do not separate and have no contacts with other partners. In models without pair formation susceptible individuals are always at risk for a new infection. Each sexual contact is with a new partner. The new model considered so-called SIS infections, i.e. there is no immunity and infected individuals ( $I$ ) who recover are susceptible again ( $S$ ).

The pair formation was modelled by a symmetric homogeneous function of degree one. For further studies on models with pair formation, the reader is referred to [Hadeler, Waldstätter, and Wörz-Busekros \(1988\)](#) and [Hadeler \(1989\)](#).

The transmission model involved eight types of individuals, since each individual is characterized according to three dichotomous variables: gender (female, male), pairing status (single, paired) and infection status (susceptible, infected). The death rates may depend on gender and on infection status. There are four types of pairs: both partners susceptible, only female infected, only male infected, both partners infected. The separation rate of a pair is allowed to depend on the type of a pair. A pair starts with one sexual contact. During a partnership sexual contacts take place at a constant rate and the probability of infection per sexual contact may depend on the gender of the infected partner. Also the recovery rates may depend on gender. The population's demography is described by an immigration-death process. An explicit threshold condition is derived for the existence of a stationary infected state which allows to assess the sensitivity of the endemic level with respect to the individual model parameters.

[Hadeler and Ngoma \(1990\)](#) replaced the immigration-death process by a birth-and-death process, where the birth rate depends on the number of pairs, and they derived explicit conditions for the bifurcation thresholds.

[Kretzschmar and Dietz \(1998\)](#) studied the effect of pair formation and variable infectivity on the spread of an infection without recovery. For the same basic reproduction number the endemic equilibrium prevalence is higher in a model with pair formation compared to a model without pair formation.

Müller and Haderler (2000) investigated the effect of pair formation and variable infectivity during the infectious period on the basic reproduction number of a sexually transmitted disease. The authors showed that, for constant separation rates of pairs, the basic reproduction number depends in a monotone way on the infectivity. They gave, however, a counter example for this monotonicity when the separation rate of a pair with two infected partners is zero if the times of their infections nearly coincide.

Eames (2006) uses models with pair formation to study strain competition. In contrast to classical models without pairs, partnerships may have an effect on the success of pathogen strains. For low separation rates, strains must have a long infectious period in order to persist.

For gonorrhoea, chlamydia and HIV Ong, Fu, Lee, and Chen (2012) compare models with and without pair formation with respect to prevalence and the critical level of condom use and concluded that it is important to account for the effects of the durations of partnerships and of the gaps between partnerships.

Kretzschmar and Heijne (2017) provide an excellent review of pair formation models for sexually transmitted diseases in general and in particular for chlamydia infection.

#### 4. Predator-prey populations with parasitic infections

Haderler and Freedman (1989) analysed in detail a model for the interaction of predator-prey populations under the influence of a parasite. The four populations uninfected and infected prey, uninfected and infected predator are described by differential equations. Therefore models are much more complicated than the usual two-dimensional predator-prey models where the Poincaré-Bendixson theorem applies. Once infected both the prey and the predator remain infected, such that the model assumes an SI type infection. They consider examples where the predation transmits the parasite to the predator. The parasite may make the prey more prone to predation. The prey may be infected indirectly from the predator through the environment.

The authors distinguished two situations: either a parasite invades an existing predator-prey system or only the parasite enables the co-existence of predator and prey. For the first situation they derived threshold conditions for the transmission parameters which ensure an infected attractor. For the second situation they gave threshold values for the parasite-mediated coexistence of predator and prey. As example for such a situation they mentioned isolated wolf populations that can survive on heavily infected moose populations in the presence of the dog tapeworm *Echinococcus granulosus*.

With 285 citations according to ResearchGate in June 2018 this paper is quoted most frequently among all papers of KP Haderler. The mathematical analysis of ecological systems under the influence of parasites is a very active field of research. Roberts and Heesterbeek (2013) illustrate the calculation of the basic reproduction number  $R_0$  with the next generation matrix approach. Selakovic, de Ruiter, and Heesterbeek (2014) provide a survey of 124 papers about the role of infectious disease agents in food webs and ecosystems.

#### 5. Demography and epidemics

Busenberg and Haderler (1990) considered an infection with waning immunity (SIRS). They study a model which is homogeneous, i.e. the equations remain the same when the size of the population changes, i.e. the model is scale-independent. The birth and the death rates depend on the epidemiological status  $S$ ,  $I$  or  $R$  of the parent. The model includes vertical transmission, i.e. infected individuals give birth to infected newborns. They determine a critical level for a unique infected persistent solution: the sum of the contact rate and the vertical transmission rate has to exceed the sum of the growth rate of susceptible individuals and the inverse of the duration of the infectious period. In the opposite case the uninfected persistent exponential solution is exponentially stable and attracts all solutions.

Thieme (1992) also addressed the interaction of demography and a potentially fatal epidemic. He considered a general contact rate which depends on the total size of the population. In some aspects Thieme (1992) is more special than Busenberg and Haderler (1990) because it is assumed that there is no vertical transmission, that all individuals have the same birth rate and that the mortality of only the infected individuals is affected. It is shown that the demography and the epidemic strongly depend on the assumptions about the contact rate  $C(N)$  as a function of population size  $N$ . The following scenarios are possible: the infection dies out and the population grows exponentially according to the difference of the birth and the death rate; there is an asymptotically exponential solution with a positive rate of increase but less than the infection-free solution; there is an infected stationary state; there is a decaying infected asymptotically exponential solution. Only  $C(0)$  and  $C(\infty)$  determine the asymptotic behaviour of the endemic.

In Haderler, Dietz, and Safan (2016) the model of Thieme (1992) is reparametrized. Instead of the excess mortality of infected individuals the case fatality proportion is used which is the probability of death of an infected individual disregarding the general death rate of susceptible and immune individuals. By introducing the inverse of the total population size and a monotone function of the case fatality the derivation of the asymptotic results is simplified. For the case of no recovery two infected solutions do exist.

#### 6. Backward bifurcations in epidemic models

The papers by Haderler and Castillo-Chavez (1995) and Haderler and van den Driessche (1997) were the first which used the term backward bifurcation in the abstract or in the title or as keywords of an epidemiological model. (See also the valuable

recent review of mathematical epidemiology by Brauer, 2017). A Web of Science search in June 2017 for the topics “backward bifurcation” AND (“epidem” OR “endem” OR “infect”) yielded 358 articles. About 90% of them appeared since 2007. (Multiple infected equilibria had been found earlier, e.g. Liu, Hethcote, & Levin, 1987, Huang, Cooke, & Castillo-Chavez, 1992).

Hadeler and Castillo-Chavez (1995) studied the transmission of an STD in a core group. They consider two versions of their model: (i) a core group of constant size and (ii) a core group of variable size where the recruitment rate decreases with the number of infected individuals in the core group and with the size of the core group. For both model versions the following assumptions are made: within the core group there is a subgroup of individuals with a reduced risk of being infected which the authors call educated or vaccinated. In their model the STD is an SIS infection, i.e. there is no immunity; infected individuals return either to the fully susceptible or to the susceptible state with reduced risk. This aspect of the model is typical for situations with backward bifurcations: the susceptibility of recovered individuals differs from the susceptibility of individuals who have not yet been infected (Safan & Dietz, 2009; Safan, Heesterbeek, & Dietz, 2006). A program of risk reduction may transfer susceptible individuals directly into the class of individuals with reduced risk.

A threshold condition for the stability of the uninfected stationary solution and a critical transfer rate from the susceptible state into the state of reduced risk in order to eliminate the infection is derived. If the protection is complete, then there is no backward bifurcation. The authors gave explicit conditions for the occurrence of backward bifurcation. In these cases positive endemic equilibria exist for values of the basic reproduction number less than one.

Hadeler and van den Driessche (1997) extended the previous model and the results to an infection with a temporarily immune state, i.e. they considered an SIRS model. The population is divided into two social groups without differential mortality due to the infection. By a singular perturbation the SIRS model is transformed into an SIS model.

In the meantime backward bifurcation phenomena have been shown to exist not only in models for STDs, but also for diseases like tuberculosis, dengue and malaria (see Gumel, 2012). Buonomo (2015) formulates a general criterion which gives sufficient (resp. necessary) conditions for the occurrence of forward (resp. backward) bifurcations.

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