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Thresholds in the Optimal Treatment of Infected Heterogeneous Populations

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Statutory Declaration

I declare in lieu of an oath that I have written this master thesis myself and that I have not used any sources or resources other than stated for its preparation. This master thesis has not been submitted elsewhere for examination purposes.

Vienna, on December 9, 2013

Contents

Abstract

This thesis investigates thresholds in an epidemic, heterogenenous model and how they are influenced by the heterogeneity. First aepidemical models is introduced, where it could be optimal to treat at a maximal possible level or not to treat at all, depending on the particular parameters and initial state. Therefore an homogeneous epidemiological model is presented, whose heterogeneity is introduced with respect to the time the individual is already infected. Afterwards the optimal control problem is introduced for a restricted, constant control variable.

The fourth section presents thresholds, firstly in a homogeneous version of the heterogeneous model. Based on these results, heterogeneity is introduced to the model and it is investigated how the thresholds are changing for different distribution functions. Finally a sensitivity analysis is conducted with respect to the infectivity of the disease.

Abstract

Diese Diplomarbeit untersucht Schwellenwerte in einem epidemiologischen, heterogenen Model und wie diese durch Heterogenität beeinflusst werden. Zuerst wird ein Problem eingeführt, bei dem es optimal sein könnte die Infizierten mit einem maximal möglichen Level zu behandeln oder gar nicht zu behandeln, was abhängig von den Parametern und dem Anfangszustand ist. Daher wird ein Model dargelegt, dessen Heterogenität bezüglich der Zeit eingeführt wurde, die das jeweilige Individuum infiziert ist. Anschließend wird das zugehörige optimal Kontrollproblem eingeführt für eine konstante Kontrollvariable. Der vierte Abschnitt präsentiert Schwellenwerte, zuerst für eine homogene Version des heterogenen Models. Basierend auf diesen Resultaten, wird Heterogenität in das Model eingeführt und untersucht, wie sich diese Schwellenwerte für verschiedene Distributionsfunktionen ändern. Zum Schluss wird eine Sensitivitätsanalyse durchgenommen bezüglich der Infektiosität der Krankheit.

1 Introduction

Within epidemiological models (for instance for animal populations) there often occurs the dilemma, whether it is better to treat the infected population or to let them die knowing that a certain part of the population is infected with a lethal disease. We have to resolve this problem for conditions, although just insufficient information is available. Moreover, there is only aggregated data available, which is not structured along the infection time (so the time since when the individual has become infected), or along other parameters of heterogeneity.

The aim of this work is to investigate under which conditions a dilemma like this can appear and how to resolve it, using the aggregated information only. Furthermore we analyse in what direction this insuffiency of information may influence our decision made on those aggregated (homogeneous) models.

Former studies already presented different types of epidemic models, as in [4], [5],[6] [7] or [8]. Generally, an aim of homogeneous epidemic models is to represent the dynamics of populations, which are divided into infected individuals (of a certain disease) and susceptible individuals, which are still not infected, but could become, so they are susceptible to the disease. These populations can be affected by one or more different diseases, which will influence the population (amount of $I(t)$ and $S(t)$) and the population size. Therefore the dynamics will be dependent on different parameters, like the strength of infectivity (thus infectiousness) of a disease, birthrate of the susceptible population, mortality rates of susceptible, non-infected individuals or infected individuals, the recovery rate, the rate of the susceptible newborns by infected mothers or the fertiltiy rate of the infected population.

In section 2.1 of this work we will introduce a general model and afterwards restrict our main model to be considering a disease without recovery of the infected individuals. We will let the mortality rate of the susceptible individuals be equal to the fertility rate, which means that in the main model we will consider a model, whereas its dynamics just regards the impact of the disease itself. Without the disease the population would be equal to the initil size, as the number of the offsprings would be equal to the number of deaths in a period.

Furthermore in all of the models shown in this thesis, the objective is to maximise the total population in the long run, without considering possible costs for the control.

Investigations about homogeneous epidemic models have already been made, in which a so called threshold point (so an intersection point between two different treatments depending on the percentage of infected individuals) occured (in [16]). Based on these results, we present in section 2.1 a simple epidemic model that represents the dynamics of a population with infected individuals $I(t)$ and individuals that are susceptible to a certain disease (we denote these individuals with $S(t)$). In contrast to the objective function used in diploma thesis [16], we let the objective function here be dependent on the control as well, therefore dependent on the mortality rate of the infected individuals. Furthermore we will not show threshold points in this model as their existence was already shown in previous research.

We introduce a specific type of heterogeneity in the model. Heterogeneity has already been introduced in [10], [12], [13] or [14] in different ways. We will regard the general case in section 2.2. In comparison to a homogeneous epidemic model, a heterogenous model represents a heterogeneus population by implying a distributed parameter system. Former studies include heterogeneity by introducing the parameter α, which is the time the individuals has already been infected, like [1] or [9]. We also integrated this method into our model, to represent heterogeneity (in 2.3).

In the third section we introduce an optimal control problem by introducing an objective function and a control. Afterwards we will show the existence of a solution of the heterogeneous model by using results from [2]. The last step in this section will be to built the heterogeneous model, we will use further on in section 4 and to restrict the optimal control problem to constant controls only, based on previous investigations in [16].

One of the aims of the fourth section will be to find thresholds by chosing parameters. Firstly the meaning and importance of threshold points is explained and afterwards thresholds will be shown for the heterogeneous model from 3.3. Therefore we will regard three different cases, which will as well lead to three different thresholds. For the first investigations here, we will choose a homogeneous version of the heterogeneous model, thus to let the distribution function be constant and not dependent on infection time α.

Afterwards heterogeneity is introduced by choosing different distribution functions, which will effect the threshold point. The distribution functions will reflect how the disease is spreading dependent on the infection time α, whereas it is important to notice that such a distribution function is generally not known beforehand. We will choose 8 different distribution function to

show 8 different possible situations and how the threshold points are going to be effected by their introduction into the model.

The last investigation in section 4.3, will be to make a sensitivity analysis of the thresholds, especially for a changing strength of the infectivity. The main focus will be how the threshold points are changing for an alternating infectiousness of the disease. Again we will consider the three different cases for parameters and just for the homogeneous version of the model (so with a constant distribution function).

2 A SI Epidemiologic Model

2.1 The Homogeneous Model

Introductorily we consider the simple homogeneous model in [1], which is an epidemic, homogeneous model for one infectious disease on an infinite time horizon. There are two state variables: On the one hand there is the infected population $I(t)$, which is already infected with the considered disease, whereas it is important to notice that we just regard the case for one infectious disease. On the other hand, there is the susceptible population $S(t)$, so the part of the whole population, which is not infected with the disease but is susceptible to it (therefore this model is named SI-model).

For the dynamics of this population, we will introduce among others a birth rate of the susceptible individuals, a recovery rate of the infection and a fertility rate of the two different individuals. Other important parameters will be the mortality rate of the infected individuals and the net mortality rate (which is the mortality rate minus the fertility rate) of the susceptible individuals.

As we just need the dynamics of this model for our results later on, we will now regard $\dot{S}(t)$ and $\dot{I}(t)$ without control variable and objective function.

The dynamics is given by the equations:

$$\begin{aligned}
\dot{S}(t) &= -\sigma \frac{I(t)S(t)}{S(t)+I(t)} + \lambda(S,I)S(t) + \gamma(S,I)I(t), && S(0) = S_0,\\
\dot{I}(t) &= \sigma \frac{I(t)S(t)}{S(t)+I(t)} - \delta(S,I)I(t), && I(0) = I_0,
\end{aligned}$$

where

- $S(t)$ is the size of the susceptible population dependent on time t (state variable)
- $I(t)$ is the size of the infected population dependent on time t (state variable)
- σ is the strength of the infection
- $\lambda = \eta - \mu$
- η is the birthrate of susceptibles

- μ is the net mortality rate of susceptible, non-infected individuals, whereas $\mu \geq 0$
- $\gamma = \nu + \epsilon\tilde{\eta}$
- ν is the recovery rate
- $\epsilon \in [0, 1]$ is the rate of susceptible newborns by infected mothers
- $\tilde{\eta}$ is the fertility rate of the infected individuals
- $\delta = \tilde{\mu} + \nu - (1 - \epsilon)\tilde{\eta}$
- $\tilde{\mu}$ is the mortality rate of the infected population

2.2 Introducing Heterogeneity with respect to Individual Features

In this section we will introduce heterogeneity like in [1] or [11] (in these works heterogeneity is introduced for individual features). Therefore we have to change the dynamics, which will here include the parameter $\tilde{p}$, the average level of risk of the population, depending on the average intensity. The other parameters will be the same as in 2.1.

The dynamics will be described by the following equations:

$$\dot{S}(t) = -\sigma\tilde{p}\frac{I(t)S(t)}{S(t)+I(t)} + \lambda(S,I)S(t) + \gamma(S,I)I(t), \qquad S(0) = S_0,$$
$$\dot{I}(t) = \sigma\tilde{p}\frac{I(t)S(t)}{S(t)+I(t)}) - \delta(S,I)I(t), \qquad I(0) = I_0.$$

In order to introduce heterogeneity to the population, we now consider the parameter $\tilde{p}$ to be specific for each susceptible individual, therefore is an individual average level of risk. $\tilde{q}$ is the same parameter for infected individuals. Moreover we introduce the variable ω, that describes individual characteristics of each individual due to the disease. Like in [1] and [11] we name this variable h-state (short for heterogeneity state).

Correspondingly two new functions are introduced:

- $\overline{S}(t, \cdot)$ is the density of the susceptible population at time t
- $\overline{I}(t, \cdot)$ is the density of the infected population at time t

Their integrals are the total size of the susceptible and infected individuals at time t. Hence for $\omega \in \Omega$, where is Ω is a measurable subset of a finite dimensional space, and $\overline{S}(t,\cdot) : \Omega \to \mathbb{R}$, $\overline{I}(t,\cdot) : \Omega \to \mathbb{R}$, one has:

$$S(t) = \int_\Omega \overline{S}(t,\omega)d\omega, \tag{1}$$

$$I(t) = \int_\Omega \overline{I}(t,\omega)d\omega. \tag{2}$$

As $\tilde{p}$ and $\tilde{q}$ are dependent on the individual as well, we consider $\tilde{p}(\omega) \geq 0$ and $\tilde{q}(\omega) \geq 0$ to be the levels of risk at h-state ω.

Therefore the dynamics of the heterogeneous model is described by:

$$\begin{aligned}\overline{S}(t,\omega) = &-\sigma\tilde{p}(\omega)z(t)\overline{S}(t,\omega) - \mu\overline{S}(t,\omega)\\ &+\eta\int_\Omega \psi_0(\overline{S}(t,\omega),\omega,\omega')\overline{S}(t,\omega')d\omega'\\ &+\gamma\int_\Omega \psi(\overline{S}(t,\omega),\omega,\omega')\overline{I}(t,\omega')d\omega', \qquad (3)\\ \overline{I}(t,\omega) = &\sigma\tilde{p}(\omega)z(t)\overline{S}(t,\omega) - \delta\overline{I}(t,\omega). \qquad (4)\end{aligned}$$

The parameters μ, η, γ and δ are the same as before and independent of ω. The density $\psi_0(\overline{S}(t,\omega),\omega,\omega')$ constitutes the probability that a newborn of mother with h-state ω' has the h-state ω and density $\psi(\overline{S}(t,\omega),\omega,\omega')$ the probability that the h-state ω' of an individuals becomes h-state ω after recovery.

To explain the meaning of the term $z(t)$, we will first introduce the population, weighted with the prevalences of the susceptible population $\tilde{p}(t)$ and the infected individuals $\tilde{q}(t)$. This weighted population is given by:

$$R(t) = \int_\Omega \tilde{p}(\omega)\overline{S}(t,\omega)d\omega, \tag{5}$$

$$J(t) = \int_\Omega \tilde{q}(\omega)\overline{I}(t,\omega)d\omega. \tag{6}$$

The term $z(t)$ in the equations is the weighted prevalence, which is the rate of weighted infected individuals. It represents the infectivity of the environment the susceptible population lives in and is given by

$$z(t) = \frac{J(t)}{R(t) + J(t)} \tag{7}$$

Hence, the heterogeneous model is given by the equations (3), (4), (1), (2), (5) and (6) and the initial conditions

$$\overline{S}(0, \omega) = \varphi_0^S(\omega) S_0,$$
$$\overline{I}(0, \omega) = \varphi_0^I(\omega) I_0.$$

where S_0 and I_0 are the initial sizes of the susceptible and the infected population and $\varphi_0^S(\cdot)$ and $\varphi_0^I(\cdot)$ are the initial, probabilistic densities of their distributions.

2.3 Introducing Heterogeneity with respect to the Infection Age

In this model we consider a heterogeneity, which differs from the one in [1], presented in the previous subsection. Namely, we introduce a new variable $\alpha \in [0, \infty]$, which is the infection age, therefore the time since the individual has become infected. Generally, this variable influences the infected population through their mortality rate, which changes dependent on the time already infected. However, also the recovery rate depends on α. Therefore the infected population now is dependent on two variables: the time t and the infection age α.

Unlike the model from section 2.2, we will consider here as well the dynamics with respect to the infection time α and not just changes due to time t. That is why in this model there is a partial differential equation (PDE) needed in contrast to the ODE in the homogeneous model. Here we will built the model like in [3] and [15], where the dynamics of the susceptible population is considered just for time t and the dynamics of the infected population is given by a PDE, depending on the time t and the infection time α.

Correspondingly, we consider the mortality rate of the infected individuals as dependent on the infection age as well. This mortality rate will be given by $\mu(\alpha)$.

Just as in 2.2, $\overline{I}(t,\cdot)$, a new function for the density of the infected population, is introduced.

The integral of $\overline{I}(t,\cdot)$ on $[0,\infty)$ is the number of the infected individuals at time t.

Moreover, a function $i(\alpha)$ is introduced for the infectivity of an individual with infection age α. This function weights $\overline{I}(t,\alpha)$ with respect to α so that the weighted population of infected individuals at time t is

$$J(t) = \int_0^\infty i(\alpha)\overline{I}(t,\alpha)d\alpha.$$

In addition, the recovery rate ν is skipped for the sake of simplicity, therefore in this model there is no possibilty to recover from the disease.

This heterogeneous model is the following:

$$\dot{S}(t) = -\sigma\frac{J(t)S(t)}{S(t)+I(t)} + \lambda(S,I)S(t) + \epsilon\eta(S,I)I(t), \tag{8}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \alpha}\right)\overline{I}(t,\alpha) = -\mu(\alpha)\overline{I}(t,\alpha), \tag{9}$$

$$S(0) = S_0, \tag{10}$$

$$\overline{I}(0,\alpha) = I_0(\alpha), \tag{11}$$

$$\overline{I}(t,0) = \sigma\frac{J(t)S(t)}{S(t)+I(t)} + (1-\epsilon)\eta(S,I)I(t), \tag{12}$$

$$I(t) = \int_0^\infty \overline{I}(t,\alpha)d\alpha, \tag{13}$$

$$J(t) = \int_0^\infty i(\alpha)\overline{I}(t,\alpha)d\alpha. \tag{14}$$

Just as in the general case before, the prevalence is now $p(t) = \frac{J(t)}{S(t)+I(t)}$, hence weighted with respect to the infected population $I(t)$. Corresponding to the previous model from section 2.3, the boundary condition in this model is (11), therefore the population density $\overline{I}(0,\alpha)$ is given by the distribution function $I_0(\alpha)$, which is the density of the infected population at time 0. Usually this distribution function is not known, a fact that will be important in section 4.2, where we will introduce possible functions.

3 A Controlled Heterogeneous SI Model

3.1 The Optimal Control Problem

In this section we consider the model from section 2.3 and introduce a control and an objective function.

Just as in the simple epidemic model in [16], we will consider a control variable $\tilde{u}(t)$ that is dependent on the time and influences the mortality rate of the infected population. The variable $\tilde{u}(t)$ itself will be the mortality rate of the infected individuals, which is influenced by the level of medication of the infected individuals. Therefore $\tilde{u}(t) \in [\mu_0, \mu_1]$, which means that with an high level of medication we achieve a lower mortality rate μ_0 than without medication, which leads to a mortality rate of μ_1.

The objective is to maximise the population size in the long run and is constituted by two terms of a sum. One is the susceptible population.The other one the infected population multiplied with a term that can be considered as the net relative productivity. This term is given by the difference of the relative productivity of the infected individuals and the control variable.

The objective function itself is not dependent on costs for medication and the controls (so the level of medication) are not priced, as we will not generally not consider that case in this model.

The objective function is the following:

$$\max \int_0^\infty e^{-rt}[S(t) + (\beta - c(\tilde{u}(t)))I(t)]dt$$

where

- $\beta \in [0, 1]$ is the relative productivity of already infected individuals
- $\tilde{u}(t) \in [\mu_0, \mu_1]$ is the medication (control variable), whereas $\tilde{u}(t) = \mu_0$ means full medication and $\tilde{u}(t) = \mu_1$ means no medication
- $r > 0$ is the discount rate
- $c(\tilde{u}(t)) > 0$ is the cost medication, that ensures the mortality rate $u \in [\mu_0, \mu_1]$

3.2 The Existence of a Solution of the Heterogeneous Model

In this section we will show that there exists a solution for the heterogeneous model in 2.2 with the objective function from 3.1.

Under certain assumptions, that are fulfilled in our heterogenous model, it is shown in [2] (Theorem 1) that there exists a solution for our model for fixed controls.

3.3 The Heterogeneous SI Model in the Class of Constant Controls

In this section we will introduce some further restrictions to the model and will consider the control as constant.

The birth rate will be equal to the natural mortality rate of the susceptibles, therefore they will not be explicitly considered in the model. There is as well no recovery from the disease, which means that an infected individual will stay infected until his death. Therefore the control variable u will influence the mortality rate of the infected population but there will be no possiblity for a complete recovery.

Just as in section 2.1, the net mortality rate for the non-infected individuals μ should be as well greater than or equal to 0, so that the population is not expanding. Considering the restrictions for u in 3.1 and the fact that the net mortality rate of the non-infected population should be lower than the mortality rate of an infected indivual, we receive:

$$0 \leq \mu < \mu_0 < \mu_1$$

The new model will have the same objective function as presented in 3.1. An important difference to the control variable used in the objective function in 3.1, is that the control in this model describes something different. In 3.1 the control $\tilde{u}(t)$ is meant to be mortality rate of infected individuals, which lies between a resulting mortality rate of full medication μ_0 and of no medication μ_1, so $\tilde{u}(t) \in [\mu_0, \mu_1]$. On the other hand, the control variable out of this model will be the controlability of the net mortality rate of the infected population (this term will by given by the mortality rate dependent on infection time α minus the mortality rate μ).

Therefore we restrict the control variable to be between a high and a low level for medication

$$u \in [0, 1] \tag{15}$$

We restrict our control variable to constant controls only, because it is easier to implement. It is proven in the diploma work [16] that optimal controls are really constant under certain conditions and assumptions in the homogeneous version of the model. Here we use an a priori restricted class of control, therefore constant controls, although the assumptions are not completely fulfilled. With the constant control variable and assuming linear costs $c(u) = cu$, the objective function for computations will be the following:

$$\max \int_0^\omega e^{-rt}[S(t) + (\beta - cu)I(t)]dt$$

Furthermore we will use the term $(1 - u)$ in the model, as with this realization the meaning of u will be now $u = u_0$ for no medication, and $u = u_1$ for full medication.

The main change will be implemented in the dynamics of $\overline{I}(t, \alpha)$. In the heterogeneous model of 2.3, the differential with respect to the infection time α and the time t is just $-\mu\overline{I}(t, \alpha)$, thus is just the mortality rate of the infected population, whereas in this model this equation will be dependent on the control variable u as well. The net mortality rate of the infected population $\nu(\alpha) = \mu(\alpha) - \mu(S, I)$ multiplied with the control u, plus net mortality rate of the susceptible, non-infected population μ describes this model.

Under these assumptions and with the objective function from above, we obtain the following model:

$$\dot{S}(t) = -\sigma \frac{S(t)J(t)}{S(t)+I(t)} - \mu(S,I)S(t), \tag{16}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \alpha}\right)\overline{I}(t,\alpha) = -(\mu(S,I) + (1-u)\nu(\alpha))\overline{I}(t,\alpha), \tag{17}$$

$$\text{where} \qquad \nu(\alpha) = \mu(\alpha) - \mu(S,I), \tag{18}$$

$$S(0) = 0, \tag{19}$$

$$\overline{I}(0,\alpha) = I_0(\alpha), \tag{20}$$

$$\overline{I}(t,0) = \sigma \frac{S(t)J(t)}{S(t)+I(t)}, \tag{21}$$

$$I(t) = \int_0^\infty \overline{I}(t,\alpha)d\alpha, \tag{22}$$

$$J(t) = \int_0^\infty i(\alpha)\overline{I}(t,\alpha)d\alpha, \tag{23}$$

$$u \in [u_0, u_1]. \tag{24}$$

By the continuous dependence of the solution of (16) - (23) on the control parameter u (see [2]), our objective functional is continuously dependent on u. Since $u \in [0,1]$, which is compact, we have the existence of an optimal u.

4 Thresholds in the SI Optimisation Model

4.1 Threshold Points

Generally a threshold prevalence p is such an initial prevalence for which two different, optimal medication levels exists. On the one hand this is an important point, as the same objective value at the prevalence p where the threshold point occurs will be achieved. A threshold point is an intersection, therefore the dividing point. The better objective value will be obtained for another treatment before as after this point. For instance for our model we will investigate threshold points for the control u_0, that is no medication and which is generally the better treatment before the threshold, and u_1, which is full medication and is better for a prevalence after the threshold point.

In this section we solve the heterogeneous model from 3.3 and find such a threshold point. Furthermore we will use the time horizon ω for computations.

Moreover we will consider in this section just a homogenous version of this model to find threshold points. The mortality rate of the infected individuals will be constant in this section and the distribution function $I_0(\alpha)$ as well, hence there is no dependency on α anymore. Furthermore, we choose the infectivity function $i(\alpha)$ to be equal to 1 so that there is no weighting due to infectivity anymore and $I(t)$ is equal to $J(t)$. Heterogeneity will be introduced to the system later on.

Now we consider three different cases for parameters, which will lead to different threshold points:

4.1.1 CASE 1

The constant c in the objective function is equal to 0, which means that in this case the objective function is not dependent on the control u, therefore the medication is free. The relative productivity of the infected individuals $\beta = 0.4$ and the strength of the infection $\sigma = 0.5$. The mortality rate of infected individuals $\mu(\alpha)$ will be equal to 1 and the discount rate $r = 0.04$. The distribution function $I_0(\alpha)$ will be constant and equal to the initial prevalence p.

Moreover we just consider the case of the net mortality rate μ being equal to 0, so that without the disease, the population would be in an equilibrium and mortality is just caused by the regarded disease.

We regard the threshold point of two different controls, which will be in this case $u_0 = 0$ (no medication) and $u_1 = 0.95$ (full medication).

Calculating the results with MATLAB, we receive the following graphic:

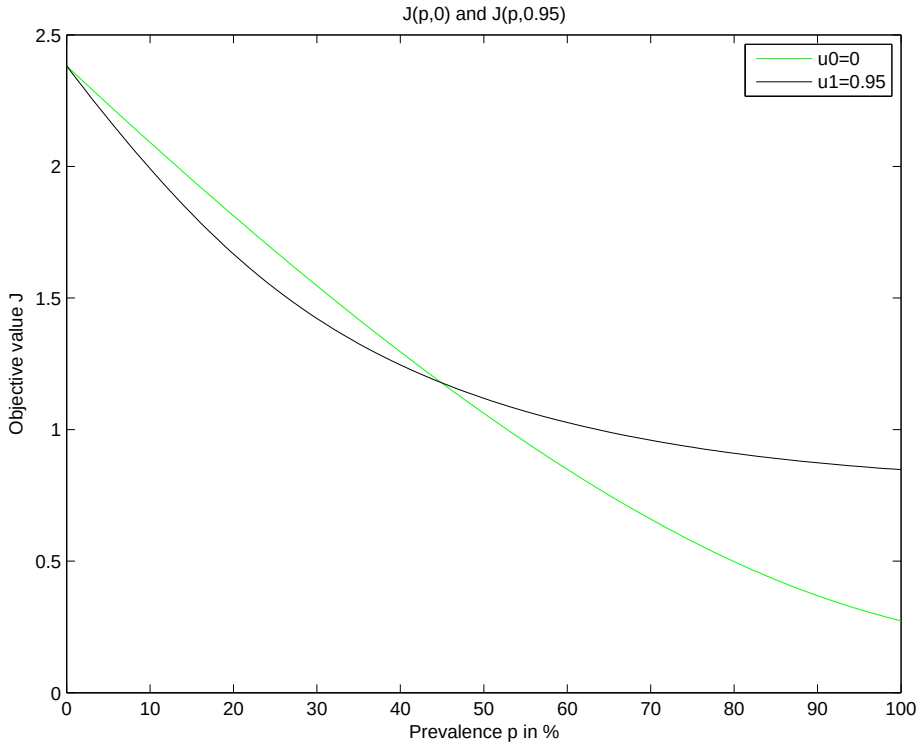

Figure 1: Objective value dependent on the prevalence for CASE 1

The threshold point occurs at the initial prevalence of about 44.91%, which means that in case that 44.91% of the total population is infected with the disease at the beginning. Again this intersection means that full treatment leads to the same value of the objective value as no medication. In the graphic it is also visible that, for a prevalence lower than 44.91%, it is better not to medicate the infected population, but to just let them die. Otherwise for a prevalence greater than 44.91% it is better to medicate the infected individuals.

4.1.2 CASE 2

In this case we take the constant c to be equal to 0.3, which means that in this case the control u is considered in the objective function as well. The relative productivity β will be equal to 0.6 and the strength of the infection

$\sigma = 0.5$. Again the net mortality rate of the non-infected individuals μ is 0 and $\mu(\alpha) = 1$. The discount rate r will be as well 0.04.

As in the case before, the two constant controls are $u_0 = 0$ (no medication) and $u_1 = 0.95$ (full medication).

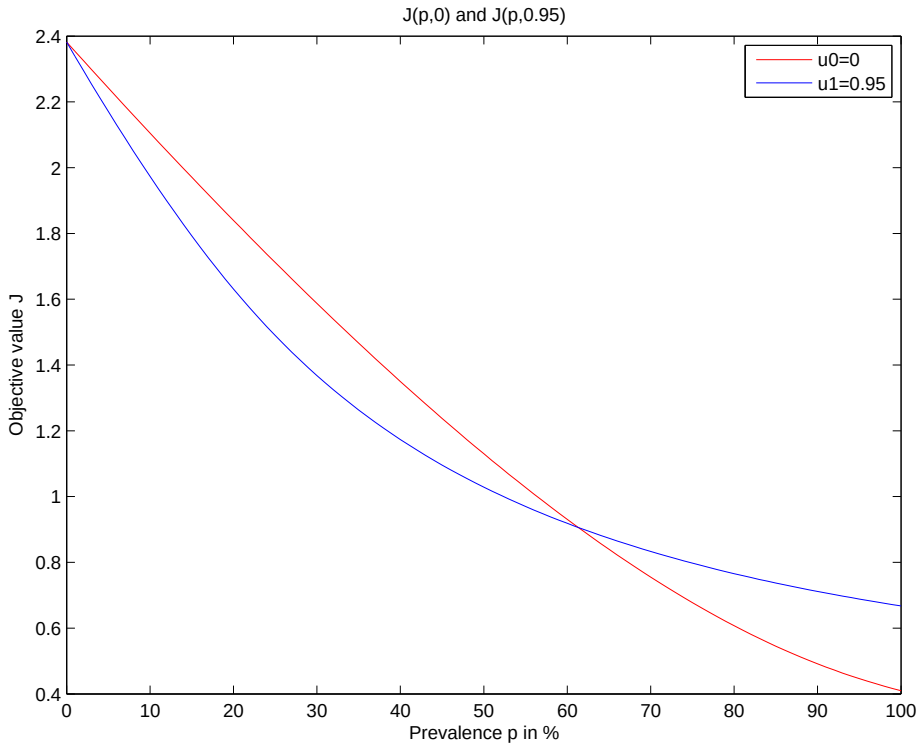

Figure 2: Objective value dependent on the prevalence for CASE 2

In this case the threshold point appears at a prevalence of about 61.33%, thus compared to the first case, the threshold point appears at a much higher prevalence. This means that in this case it is better to start treating at an even higher level of the prevalence and better to let the infected population die for a prevalence lower than 61.33%. This is to be expected since in the present case the medication is costly.

4.1.3 CASE 3

This case will basically be the same as CASE 2, with the only difference that the constant parameter c out of the objective function will be equal to 0.4. The rest will be be the same (so: relative productivity of already infected individuals $\beta = 0.6$, strength of infection $\sigma = 0.5$, net mortality

rate of non-infected individuals $\mu = 0$, mortality rate of infected individuals dependent on the age of infection $\mu(\alpha) = 1$ and discount rate $r = 0.04$).

Again the two constant controls are $u_0 = 0$ (no medication) and $u_1 = 0.95$ (full medication).

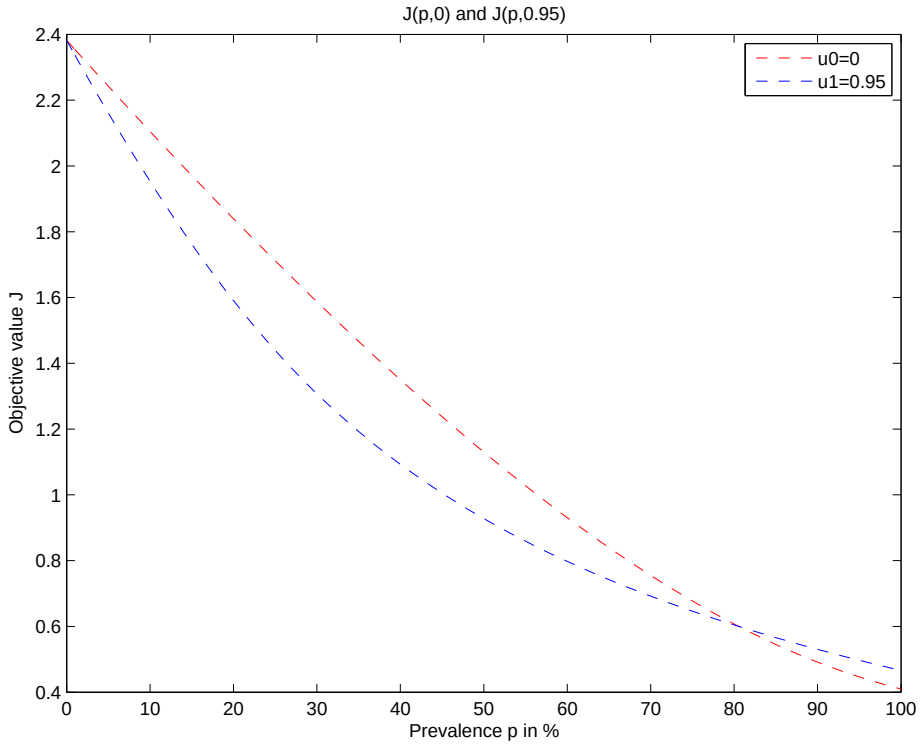

Figure 3: Objective value dependent on the prevalence for CASE 3

The threshold in this case occurs at a prevalence of about $80,56\%$, which means that in this model it is better to treat just for a very high prevalence, therefore in case that more than $80,56\%$ of the population are already infected. This case will be interesting especially in the next section.

4.2 Thresholds in a Heterogeneous Model

Until now we just found thresholds for the homogeneous versions of our model. In this section we will now concentrate on the threshold and how it is changing for different non-constant distribution functions. For the sake of comparison, here again the already located thresholds of the homogeneous version of the model with the threshold at a prevalence of 44.91% (CASE 1), 61.33% (CASE 2) and 80.56% (CASE 3).

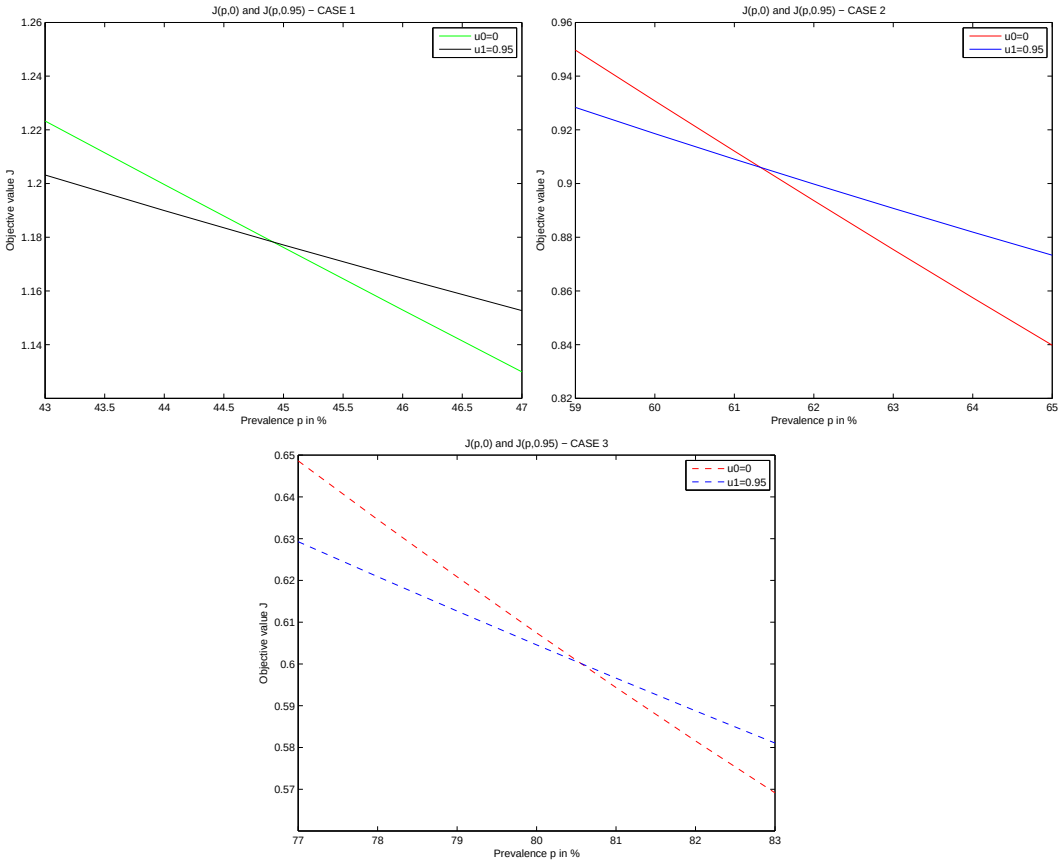

Figure 4: Thresholds for constant distribution functions for all cases

The next step will be to introduce heterogeneity by choosing distribution functions that are not constant, but have the same integral as the constant distribution function out of the last section.

As for our calculations we are considering again the time horizon ω, that is why the integral of this function is

$$\int_0^\omega I_0(\alpha)\ d\alpha = \int_0^\omega p\ d\alpha = p\omega$$

The next step will be to introduce different non-constant distribution functions for the three different cases of parameters and a comparison of the results.

4.2.1 Regarding CASE 1

The first possible distribution function we regard is linear and decreasing.

$$I_0^1(\alpha) = -\frac{2p}{\omega}(\alpha - \omega).$$

The integral of this distribution function is a well $p\omega$ and (in contrast to the constant distribution function), the population decreasing regarding the infection time α at time $t = 0$.

Calculating the threshold for CASE 1 we receive the following graphic:

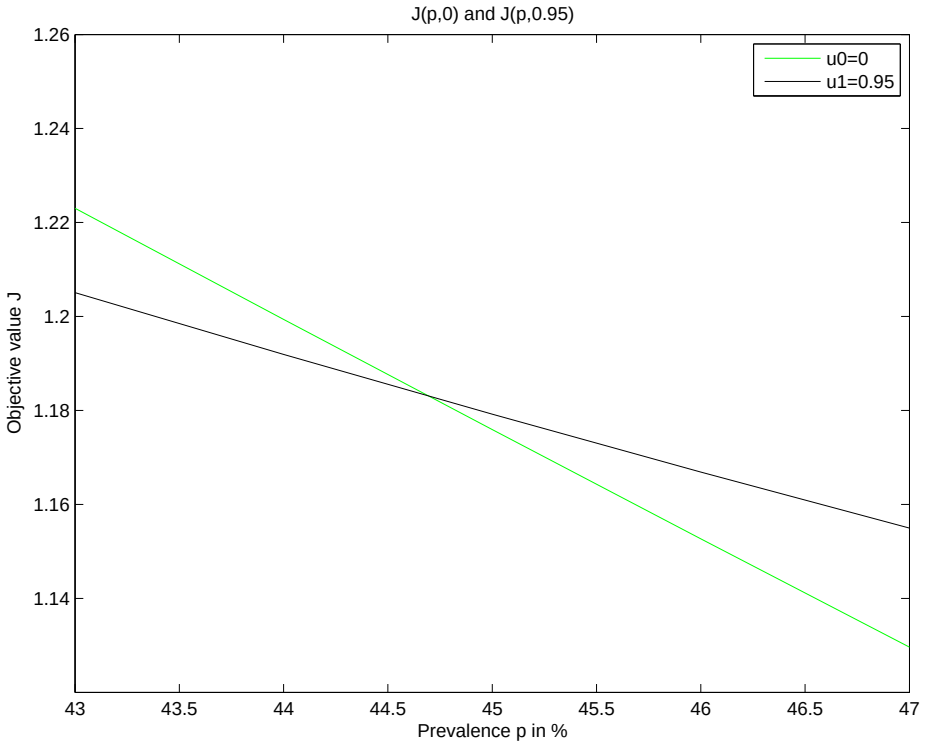

Figure 5: Threshold for distribution function $I_0^1(\alpha)$ for CASE 1

Comparing the threshold of the model with this distribution, we see that the threshold moves slightly to the left, which means that in comparison to the constant distribution function, here it is better to start treating at a lower level of the prevalence.

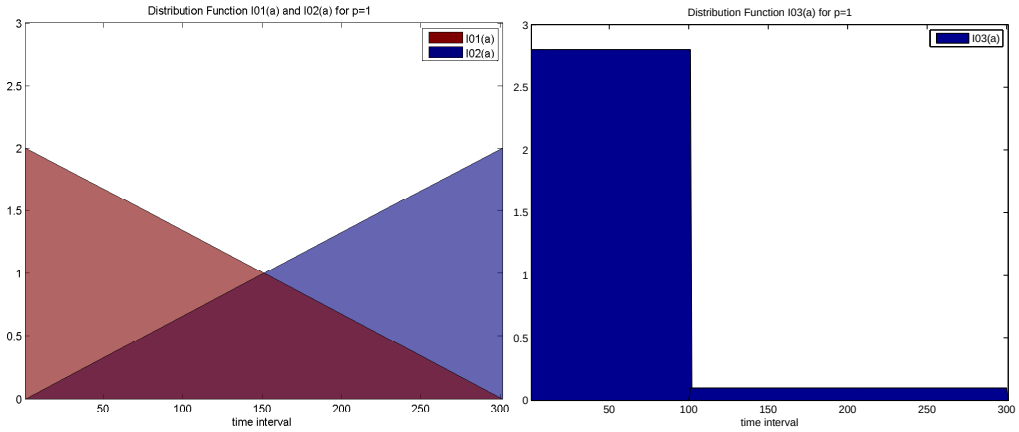

Figure 6: Distribution function $I_0^1(\alpha)$, $I_0^2(\alpha)$ and $I_0^3(\alpha)$

As a second distribution we consider a linear and increasing function:

$$I_0^2(\alpha) = \frac{2p}{\omega}\alpha.$$

Again the integral of this distribution function is $p\omega$ and compared to the distribution function $I_0^1(\alpha)$ the infected population increases with respect to the infection time α.

Calculating the threshold for CASE 1 again, we receive:

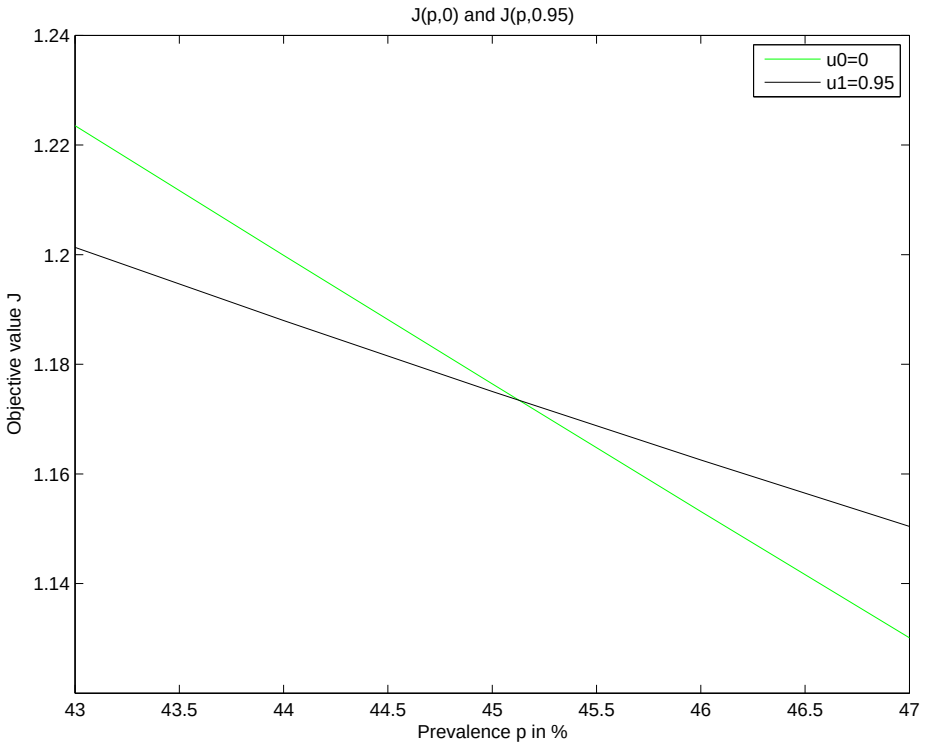

Figure 7: Threshold for distribution function $I_0^2(\alpha)$ for CASE 1

Here the threshold moves to the right, which means that in contrast to the homogeneous version of our model, it is better to start medicating the population at an higher prevalence.

The third distribution presents the case that there is a large infected population at the beginning (until $\frac{\omega}{3}$) and afterwards it decreases to a very low level with respect to infection time α.

$$I_0^3(\alpha) = \begin{cases} 3p - \frac{1}{5} & \text{for } \alpha \leq \frac{\omega}{3}, \\ \frac{1}{10} & \text{for } \alpha > \frac{\omega}{3}. \end{cases}$$

In comparison to the non-constant distribution function $I_0^1(\alpha)$, $I_0^3(\alpha)$ doesn't describe steadily decreasing infected population, but rather a disease, which is much stronger at the beginning of the time.

Calculating the threshold for the model with parameters from CASE 1 with this distribution function, we obtain:

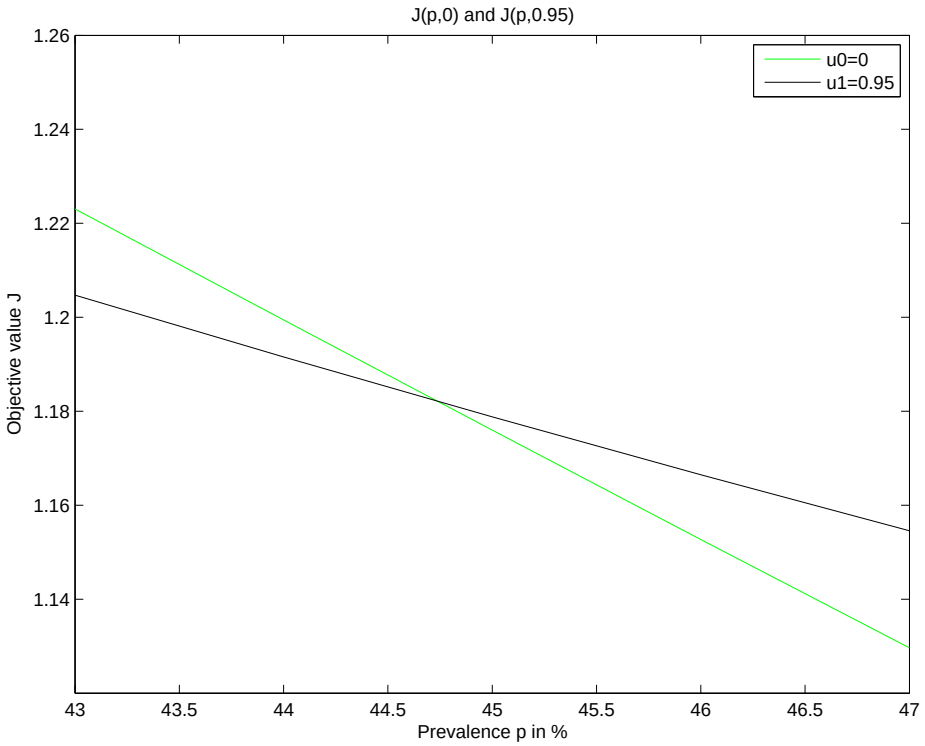

Figure 8: Threshold for distribution function $I_0^3(\alpha)$ for CASE 1

Again, like with distribution function $I_0^2(\alpha)$, we receive a threshold that is slightly more left than the threshold with the homogeneous version of the model. In this case the threshold is at about a prevalence of 44.73%.

We now investigated that in case of a disease, which breaks out rather at the end (or at the beginning) of a time interval, influences the threshold point to be rather right (or more left) in comparison to the threshold point out of the homogeneous model. This is why now we will see how an even more extreme case will influence the threshold.

The fourth distribution function $I_0^4(\alpha)$ will be the case for a strong disease at the beginning of the time interval and without fading until the end. The function is the following:

$$I_0^4(\alpha) = \begin{cases} 5p & \text{for } \alpha \leq \frac{\varepsilon}{5}, \\ 0 & \text{for } \alpha > \frac{\varepsilon}{5}. \end{cases}$$

This function again has the same integral as the constant function from

the homogeneous version.

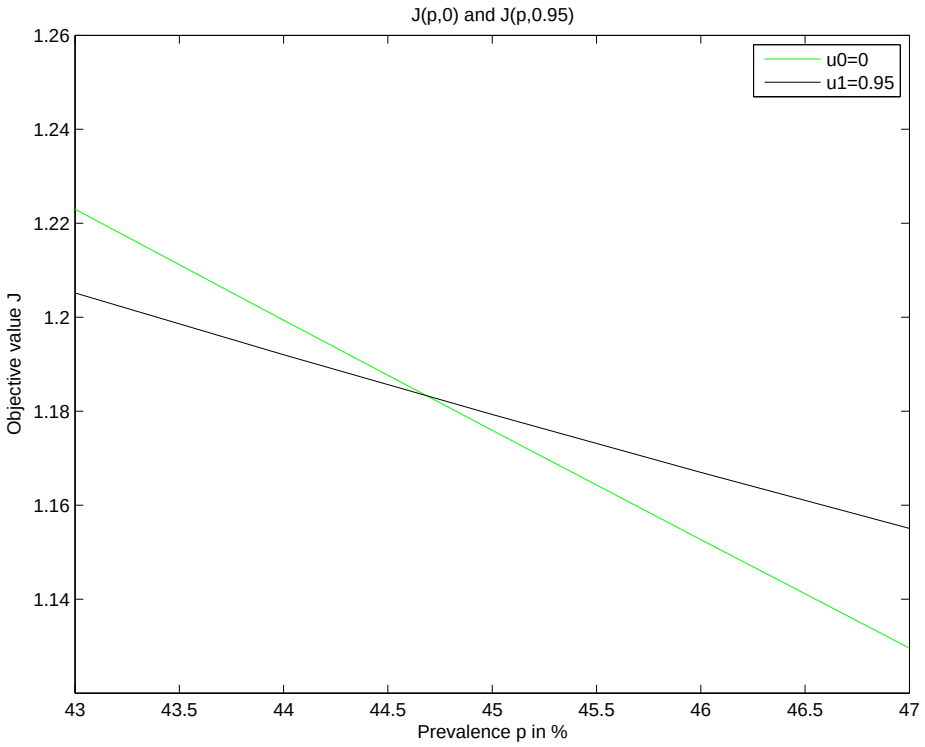

Figure 9: Threshold for distribution function $I_0^4(\alpha)$ for CASE 1

Now the threshold point is as well more left than the original one, at a prevalence of 44.68%.

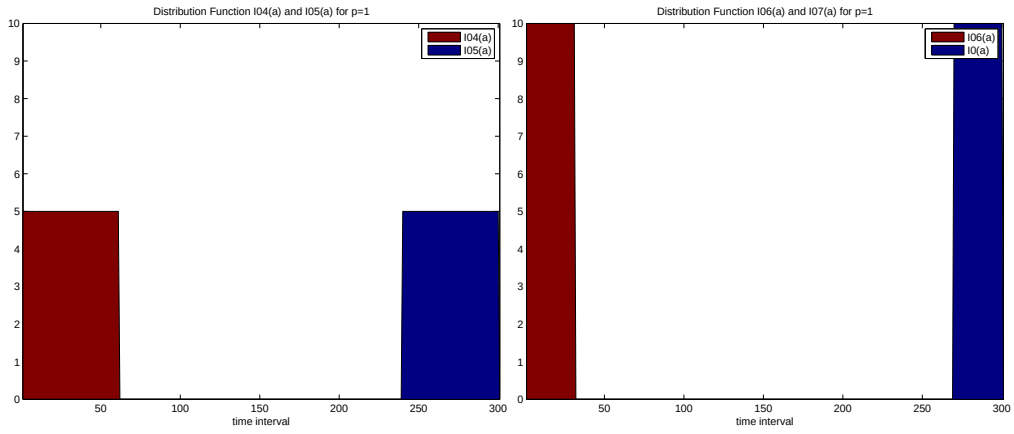

Figure 10: Distribution function $I_0^4(\alpha)$, $I_0^5(\alpha)$, $I_0^6(\alpha)$ and $I_0^7(\alpha)$

The fifth distribution function should reproduce a disease, which is strong especially at the end of the time interval.

$$I_0^5(\alpha) = \begin{cases} 0 & \text{for } \alpha < \frac{4\omega}{5}, \\ 5p & \text{for } \alpha \geq \frac{4\omega}{5}. \end{cases}$$

Calculating the threshold for this distribution function leads to:

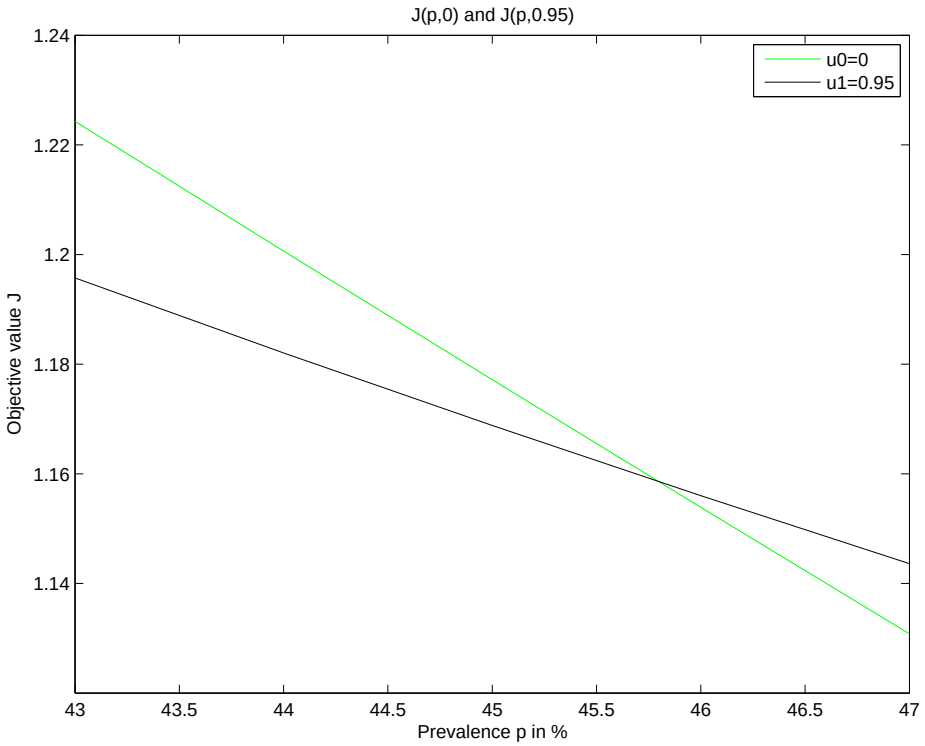

Figure 11: Threshold for distribution function $I_0^5(\alpha)$ for CASE 1

Here the shift of the threshold point to the right hand side is very clear: in comparison to the original threshold, which was at the level of prevalence of about 44.91%, the new threshold point is at a prevalence of about 45.79%.

Now we will try to achieve an even more obvious change of the threshold point, by choosing a distribution function that represents a disease that is even much stronger at the beginning of the time interval than $I_0^4(\alpha)$.

$$I_0^6(\alpha) = \begin{cases} 10p & \text{for } \alpha \leq \frac{\omega}{10}, \\ 0 & \text{for } \alpha > \frac{\omega}{10}. \end{cases}$$

With this function we receive the following graphic:

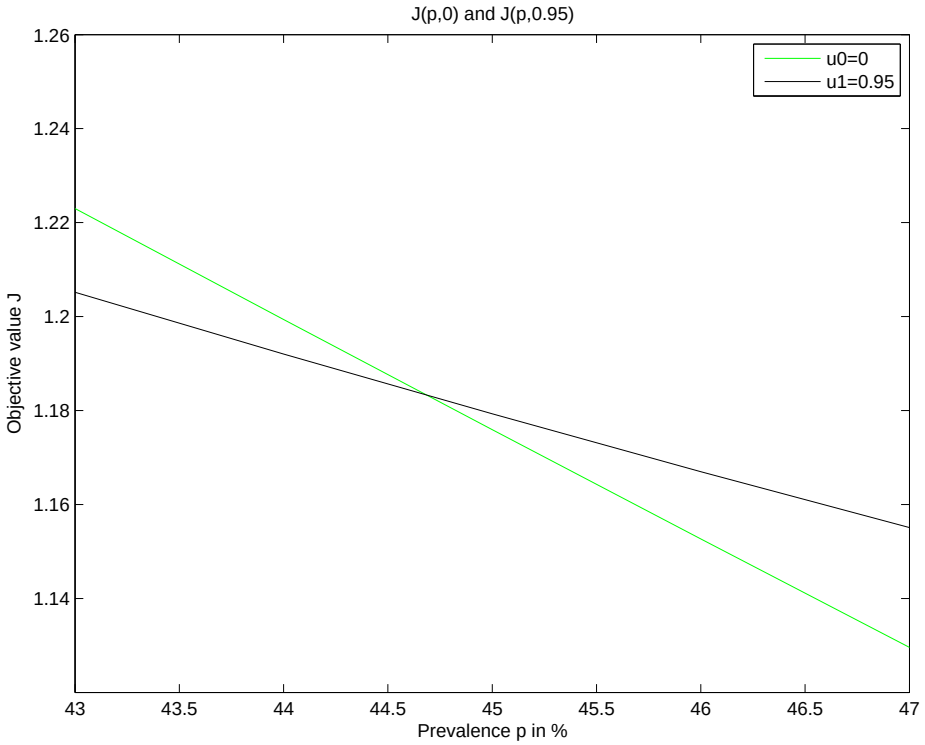

Figure 12: Threshold for distribution function $I_0^6(\alpha)$ for CASE 1

Again a shift to the right. The threshold point is now at a prevalence of about 44.67%. So in comparison to the results with the distribution function $I_0^4(\alpha)$, there was no strong change of the threshold point.

Based on the last function, the next distribution function will as well reproduce a disease, which is very strong at a certain point in the time interval, this time it is right at the end.

$$I_0^7(\alpha) = \begin{cases} 0 & \text{for } \alpha < \frac{9\omega}{10}, \\ 10p & \text{for } \alpha \geq \frac{9\omega}{10}. \end{cases}$$

Again, calculating the threshold point, we receive:

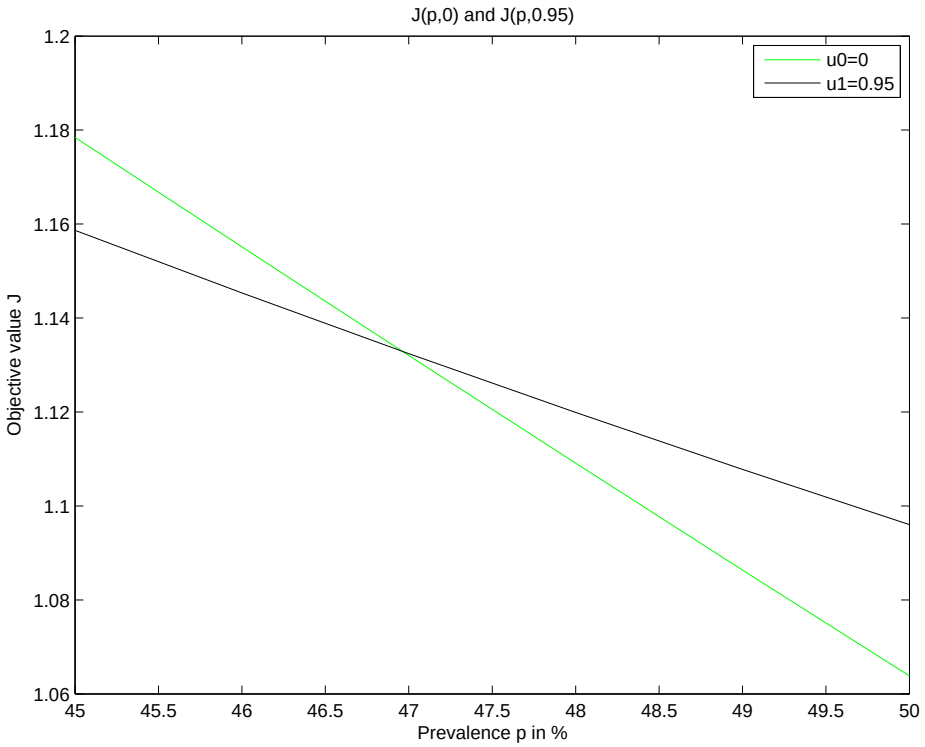

Figure 13: Threshold for distribution function $I_0^7(\alpha)$ for CASE 1

This time the threshold point moved much more to the right side.

4.2.2 Regarding CASE 2

We will make the calculations for the same distribution functions from above as well with the model with parameters from CASE 2. We received rather similar results as with CASE 1:

For distribution function $I_0^1(\alpha)$, $I_0^3(\alpha)$ and $I_0^4(\alpha)$ we received again a threshold, which is moving slightly to the left hand side. In comparison to the result we gained for the homogeneous version of the model (so a threshold at a prevalence of about 61.33%), we gained for the model with distribution function $I_0^1(\alpha)$ the threshold at a prevalence of about 61.04%, with the distribution function $I_0^3(\alpha)$ at a prevalence of 61.03% and with $I_0^4(\alpha)$ at a prevalence of 61.08%. Furthermore for distribution function $I_0^6(\alpha)$ we gained a threshold at a prevalence of about 61.01%. Obviously for an even very high peak of the infected individuals at the firsth tenth of the time

interval, the threshold is not changing very much. We see as well, that in our model we receive thresholds that are moving slightly to the left for distribution functions, which have a higher degree of infected individuals at the beginning of the disease at time 0.

The more interesting investigation for CASE 2 as well, is that for distribution functions, which represent more infected individuals at the end of the infection time (so a strong break-out of the disease right at the end of the time interval). For these distribution functions the shift of the threshold is much more significant than for the distribution functions $I_0^1(\alpha)$, $I_0^3(\alpha)$ and $I_0^4(\alpha)$.

Calculating the threshold point for the model with distribution function $I_0^2(\alpha) = \frac{2p}{\omega}\alpha$, we receive the following graphic:

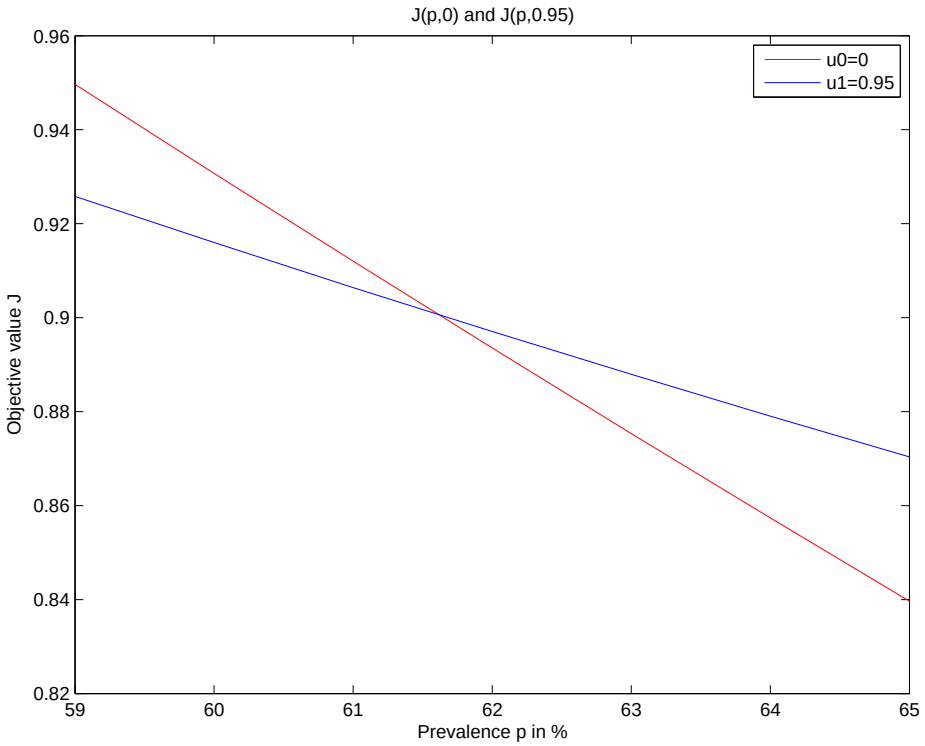

Figure 14: Threshold for distribution function $I_0^2(\alpha)$ for CASE 2

Just as the threshold point for distribution function $I_0^2(\alpha)$ in CASE 1, the threshold moved to the right and is now at a prevalence of about 61.61%. $I_0^2(\alpha)$ is linear and increasing, hence there are more infected individuals at the end of the time interval than at the beginning and the number is always increasing. Therefore in case of an increasing infected population

with respect to infection time α, it is better to start treat at an higher level of the prevalence (in comparison to the constant distribution function).

Now we consider the results for the model with distribution function $I_0^5(\alpha)$, remembering that this distribution function has an high infected population at the last fifth of the time interval.

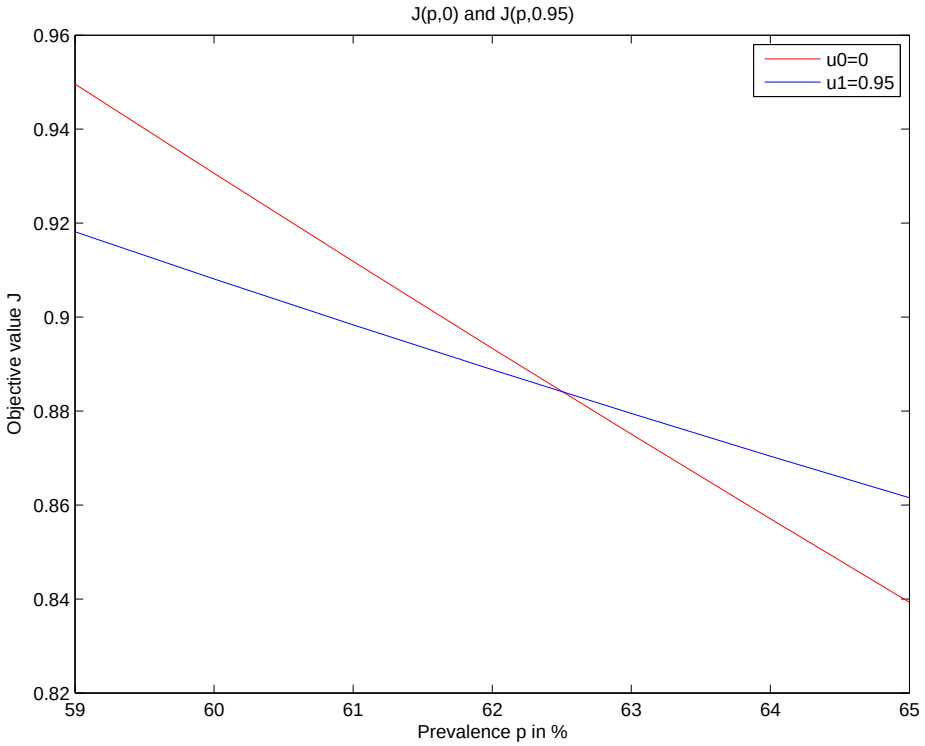

Figure 15: Threshold for distribution function $I_0^5(\alpha)$ for CASE 2

In this graphic the threshold moved to a prevalence of about 62.51%, therefore even more to the right than with distribution function $I_0^2(\alpha)$.

These results provide an incentive to consider as well the results for distribution function $I_0^7(\alpha)$, hence for a function with an extraordinary peak of the infected population (with respect to the infection time α) at the last tenth of the time interval.

Calculating the threshold for $I_0^7(\alpha)$ leads to

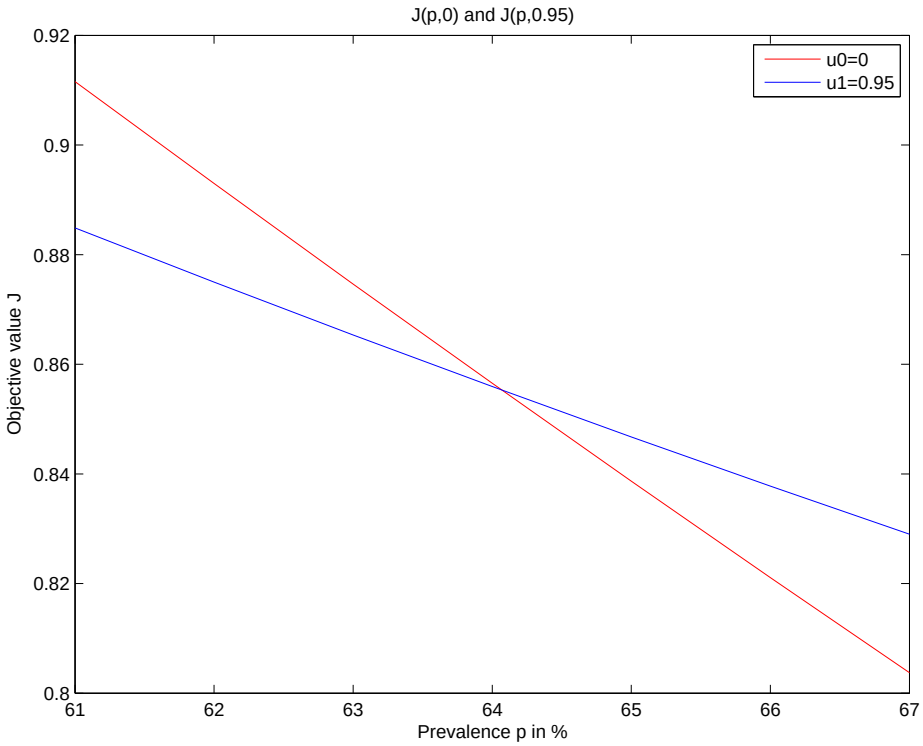

Figure 16: Threshold for distribution function $I_0^7(\alpha)$ for CASE 2

The threshold shifted until the level of the prevalence of about 64.05%, which is again a big shift in comparison to the initial model with the heterogenous model.

For CASE 2 and CASE 1, it is not possible to find an extraordinary distribution function so that the threshold disappears. We will show in the following section, that a disappearing threshold is possible under certain circumstances for CASE 3.

4.2.3 Regarding CASE 3

Generally we received similar results for CASE 3 for models with distribution functions $I_0^1(\alpha)$ (a threshold at a prevalence of about 80.14%), $I_0^3(\alpha)$ (threshold at 80.15%), $I_0^4(\alpha)$ (80.13%) and $I_0^6(\alpha)$ (80.13% as well). So again, for distribution functions with an infected population that is larger at the beginning of the time interval (with respect to infection time α), the shift of the threshold point is not very significant.

For distribution function $I_0^2(\alpha)$, we receive the following graphic:

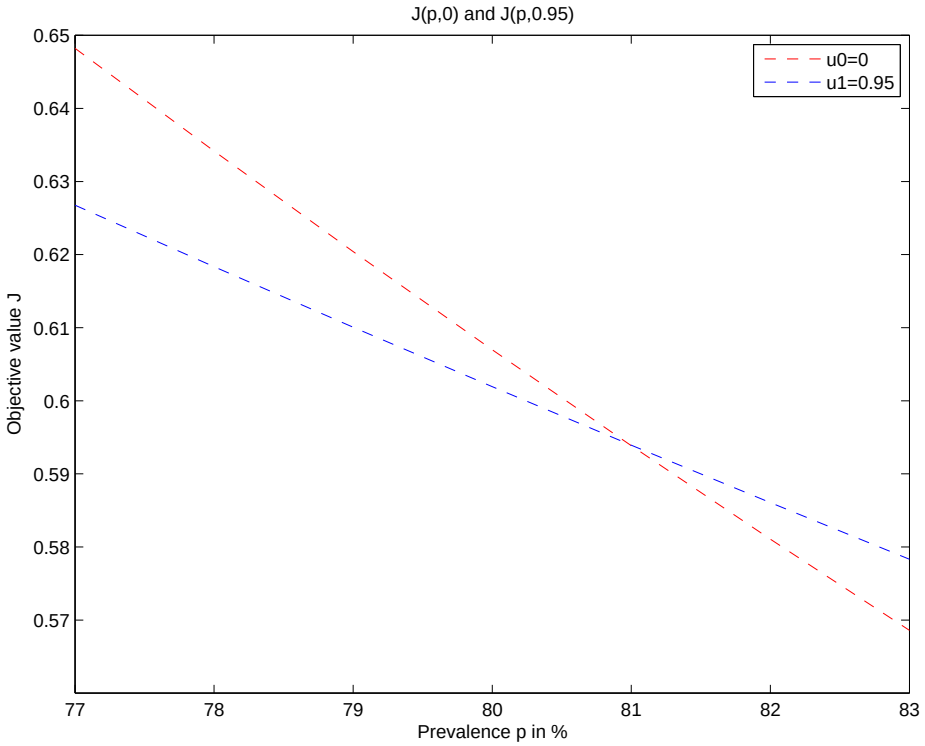

Figure 17: Threshold for distribution function $I_0^2(\alpha)$ for CASE 3

Again, the threshold point moved to the right side, from 80.56% to 80.99%. Hence for the increasing and linear case the variation is not very significant as well.

Calculating the results for $I_0^5(\alpha)$, we receive

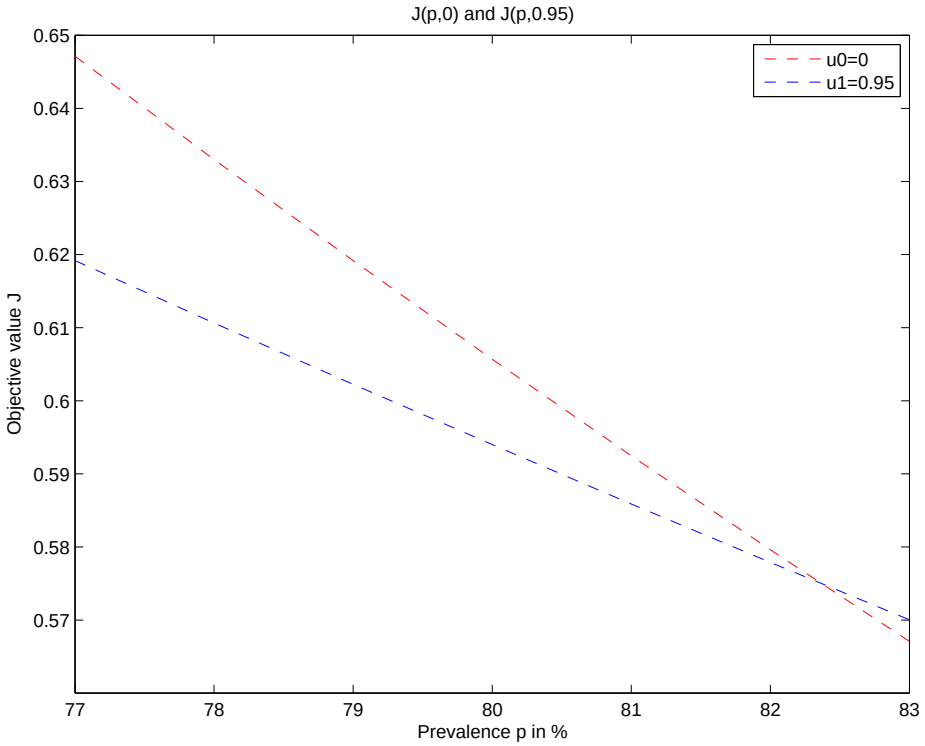

Figure 18: Threshold for distribution function $I_0^5(\alpha)$ for CASE 3

In comparison to the results from the other two cases, we receive a much more significant variation of the initial threshold point for CASE 3. Here the threshold point occurs at a prevalence of about 82.37%.

For distribution function $I_0^7(\alpha)$, we receive

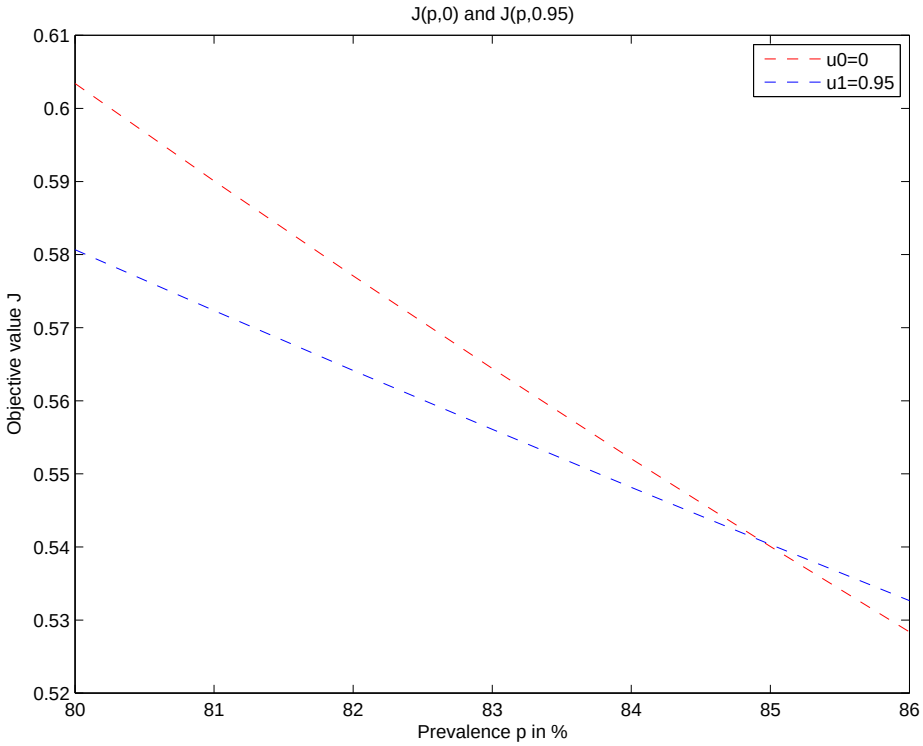

Figure 19: Threshold for distribution function $I_0^7(\alpha)$ for CASE 3

Now the threshold point is at a prevalence of about 84.93%, which offers again an incentive to introduce another extraordinary distribution function to the model, so that the threshold disappears.

This distribution function will be

$$I_0^8(\alpha) = \begin{cases} 0 & \text{for } \alpha < \frac{24\omega}{25} \\ 25p & \text{for } \alpha \geq \frac{24\omega}{25} \end{cases}$$

Plotting this distribution function:

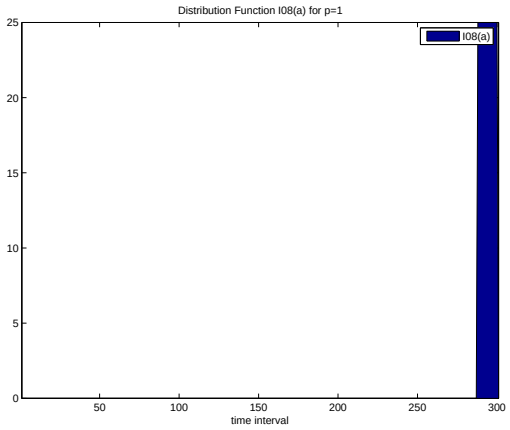

Figure 20: Distribution function $I_0^8(\alpha)$

In reality, this case is not very probable, as the outbreak of the disease is just in the last $\frac{1}{25}$ of the time interval.

Again, calculating the objective values dependent on the prevalence, we receive the following graphic:

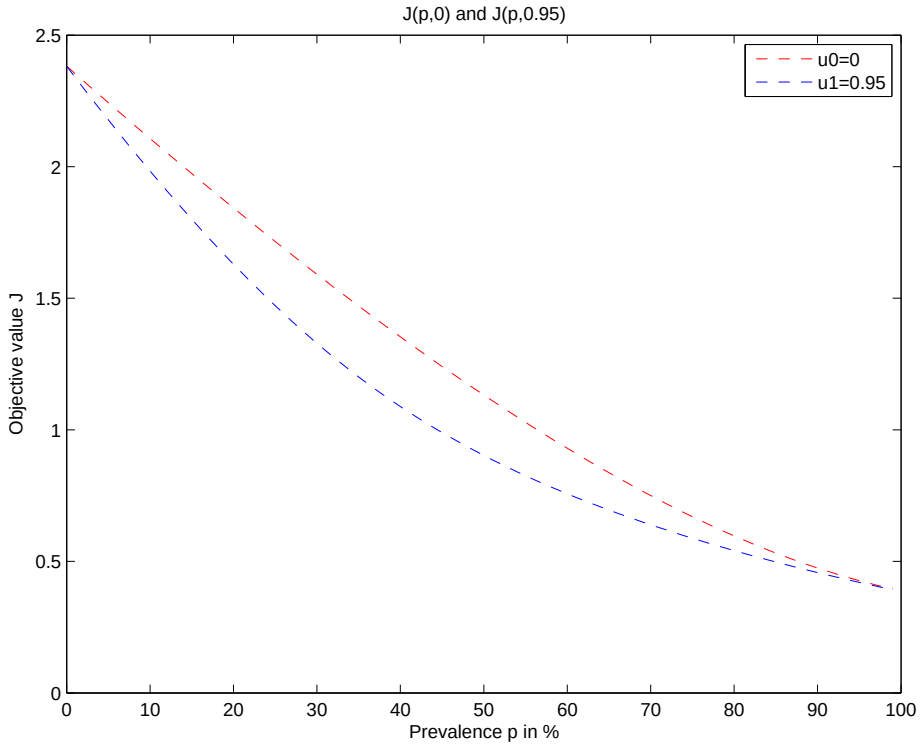

Figure 21: No threshold for distribution function $I_0^8(\alpha)$ for CASE 3

This graphic shows us, that with this distribution function, the threshold even disappeared, which means that in this case it is always better not to medicate the infected population, but to let them die. Considering our distribution function, this would mean that it is always better to let the infected individuals die, in case the outbreak of the disease is very strong and right at the end of the time interval.

4.3 Sensitivity Analysis of Thresholds in the Optimal Control of Epidemic Models

In this section we will make a sensitivity analysis for the homogeneous version of the model, especially how the parameter σ (strength of the infection) affects the threshold.

In this analysis we set the mortality rate dependent on infection time $\mu(\alpha)$ equal to 1 (so that we can compare the results from section 4.1) and we will see how σ influences the thresholds.

Again, we will consider the different cases.

Considering CASE 1

Again, in CASE 1, we are considering our model for parameters $c = 0$ (constant in objective function), $\beta = 0.4$ (relative productivity of infected individuals) and $u_0 = 1$, $u_1 = 0.95$ (controls), $\mu = 0$, $r = 0.04$ and as mentioned before $\mu(\alpha) = 1$. The only parameter we will very is $\sigma \in [0, 1]$. We already know that for $\sigma = 0.5$ our threshold is at a prevalence of about 44.91% (regarding Figure 1).

First we consider σ to be equal to 0, so that the strength of the infection is 0. Of course, this means that there is no intersection between the two curves, so that there is no threshold and it is always better to medicate.

For $\sigma = 0.1$, we receive the following graphic:

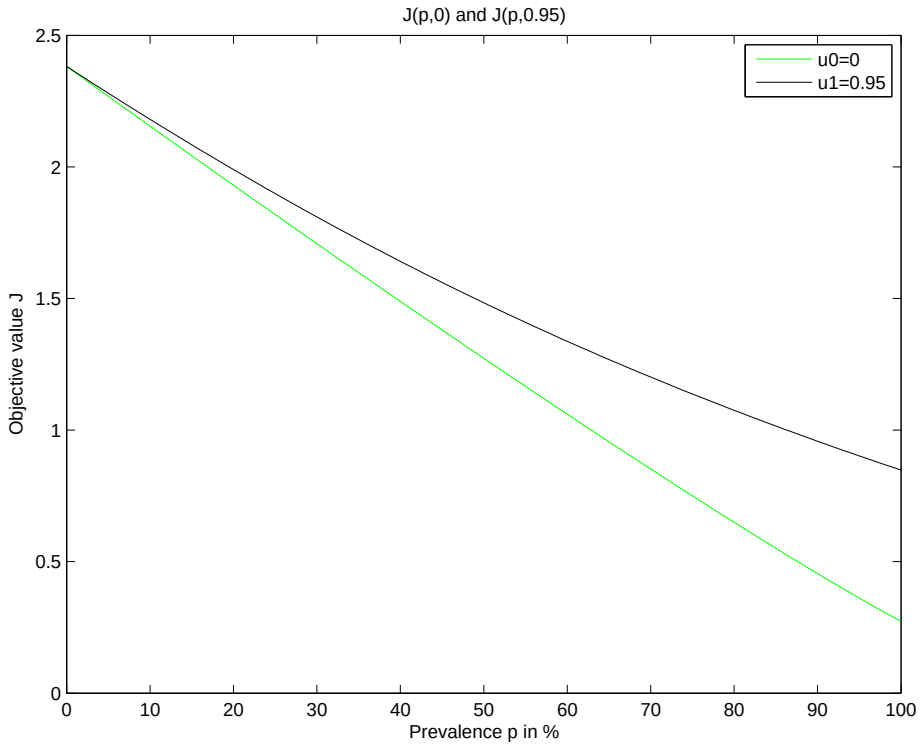

Figure 22: No threshold for $\sigma = 0.1$

There is still no intersection, which means that for a disease with a very low strength of infectivity, there is still no threshold. In this case full medication is always better, so full medication for every infected individual for all prevalences. The curve for no medication (u_0) is almost straight and decreasig.

Now we will set $\sigma = 0.3$:

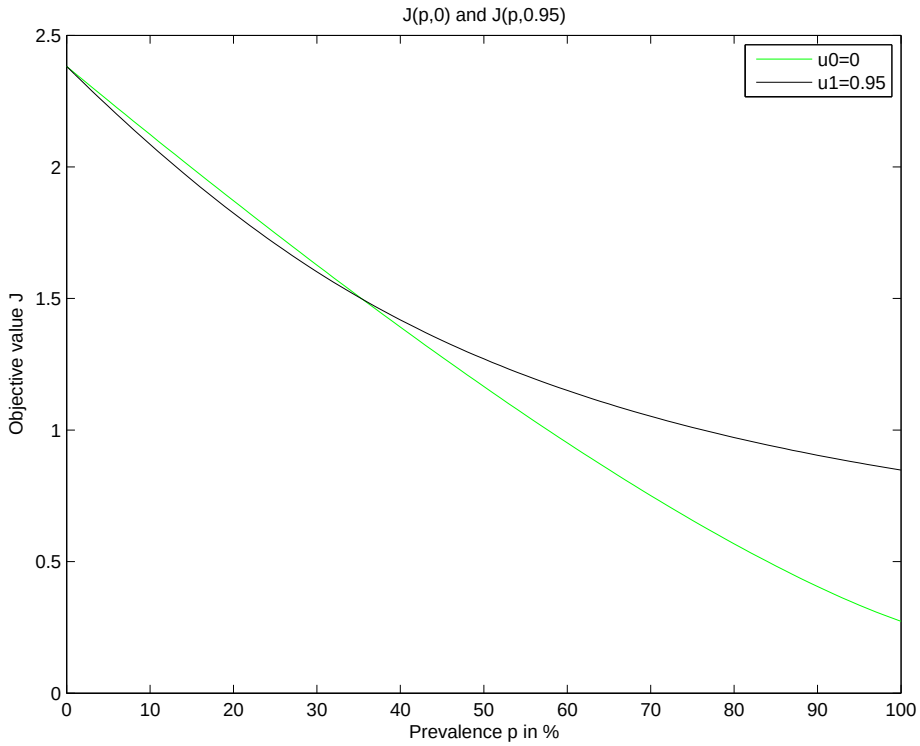

Figure 23: Threshold for $\sigma = 0,3$

In this case there is already an intersection between the two curves at a prevalence of about 35.49%. Thus for a rather low strength of infection, there is already an existing threshold. For a prevalence lower than 35.49% it is better not to medicate the infected individuals (so to let them die) and for a prevalence higher than the threshold, full medication is better. Furthermore especially the curve for u_1 is not that straight anymore. The slope of the two curves is for increasing prevalence not as high as for a low prevalence p (until about 35%). This means that for instance for u_1 the changes of the objective value are more significant for a low prevalence p than for a high prevalence with respect to σ.

The next results we regard for $\sigma = 0.6$, as this σ is very close to the σ from the original model of 4.1:

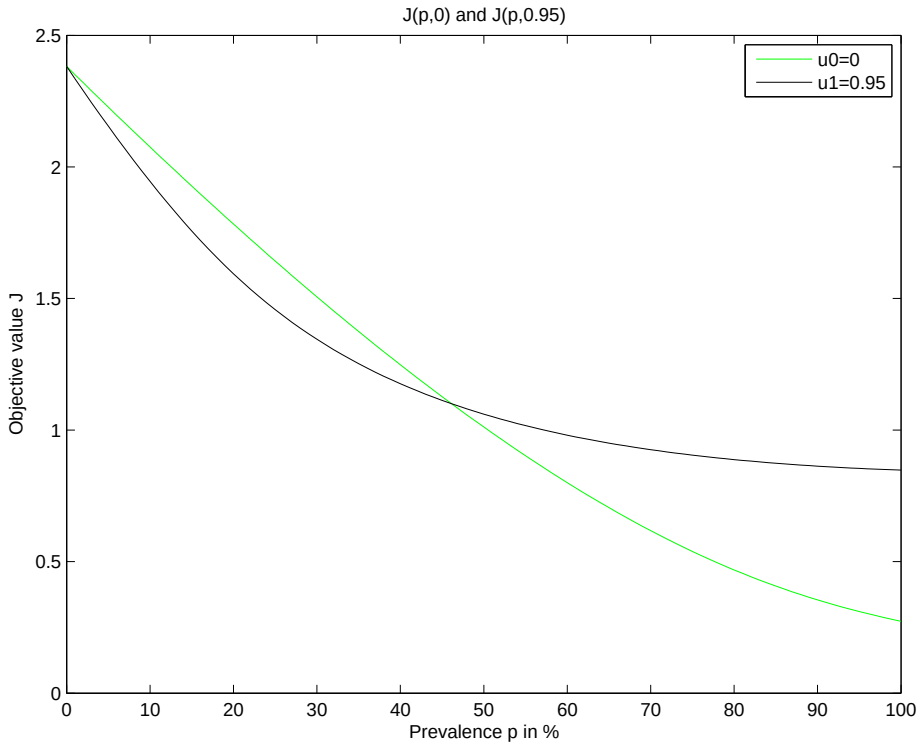

Figure 24: Threshold for $\sigma = 0.6$

Here the threshold point is quite the same as for $\sigma = 0.5$, which could be interpreted as an already decreasing growth of our threshold for increasing strength of the infection σ. The threshold now is at a prevalence of about 46.14%, which is already rather close to the threshold for $\sigma = 0.5$, which occurs at a prevalence of about 44.91%.

Probably, for an even more significant strenght of the infection, the threshold point is not varying very much anymore. To confirm this assumption we calculate the result for $\sigma = 0.8$:

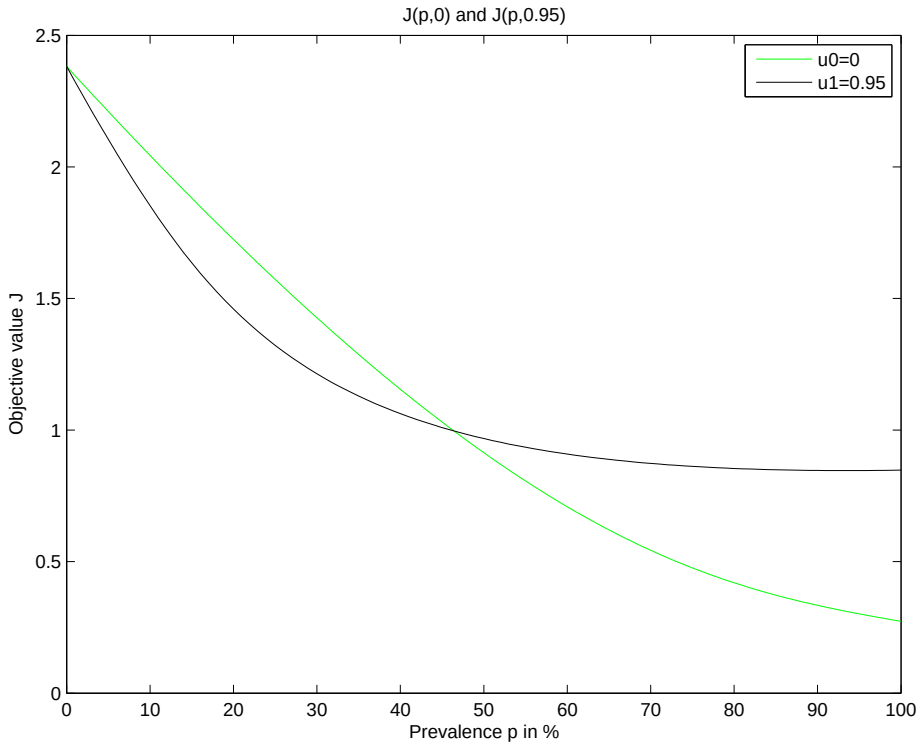

Figure 25: Threshold for $\sigma = 0.8$

In comparison to the results for $\sigma = 0.5$ or $\sigma = 0.6$, the threshold has not changed significantly, the threshold occurs at a prevalence of about $46,30\%$. The much more considerable change, is that in comparison to the other models, the slope of the curves is more decreasing for increasing σ. This could be interpreted as for an high strength the objective value (which is the number of the population in the long run), is not changing significantly for an initial infected population greater than 30% of the total population.

The following graphic, which shows the treshold point in dependency on σ, is summing up the main results of this section:

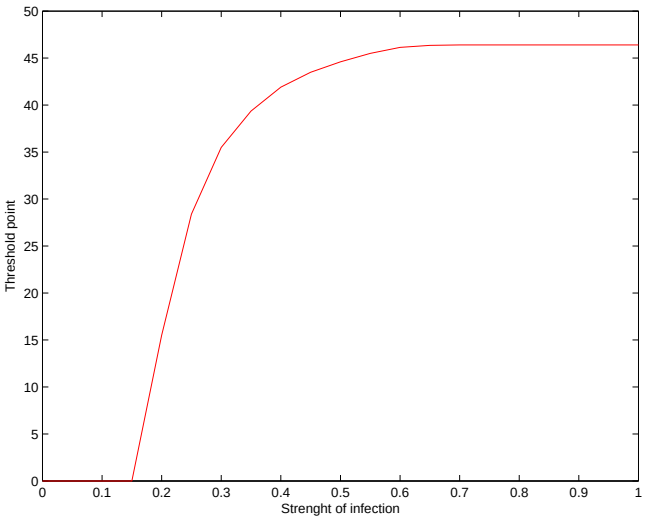

Figure 26: Threshold point depending on strength of infection σ

We see that for very small σ, there is no threshold, just the intersection of the curves at the beginning ($t = 0$). This makes sense as for a disease which has a very low strength of infection, it is always better to treat the infected individuals, thus there is no threshold. For small σ, so a strength of the infection for more than about 0.15, the threshold is increasing very much, so the threshold is changing very much for $\sigma \in (0.15; 0.5)$. This means that for diseases with a strength of the infection between 0.15 and 0.5, the point where it is equally good to fully medicate the infected individuals or not to treat them at all, is increasing until a prevalence of about 50% (so until a situation where half of the initial population is infected). Afterwards the threshold is almost not changing anymore, which means that for a disease with the strength of infection higher than 0.5 in our model, the threshold point is almost constantly at a prevalence of about 46.30%. Hence for a disease with a sufficiently high strength of the infection, it is always better to start treating for a population in which more than 46.30% are infected, and it is better not to treat for a population with an initial quote of infected individuals lower than 46.30%.

Considering CASE 2

The main difference between the parameters of CASE 1 and CASE 2 are, that in CASE 2 the relative productivity of the infected individuals β is higher (0.4 in CASE 1 and here 0.6) and that the constant out of the objective function c is not equal to 0, but 0.3. This means that for this case,

the objective function is dependent on the control variable as well, as the constant c is not equal to 0. Again the other parameters will be $u_0 = 1$, $u_1 = 0.95$ (controls), $\mu = 0$, $r = 0.04$ and a constant mortality rate of the infected individuals dependent on infection time $\mu(\alpha) = 1$.

We already know the result for $\sigma = 0.5$ as this was the result of section 4.1.2. As visible in Figure 2, the threshold occurs at a prevalence of 61.33%.

Of course in this model there is no threshold for a strength of the infection equal to 0, as it was before.

We will now investigate if there is a threshold for $\sigma = 0.1$:

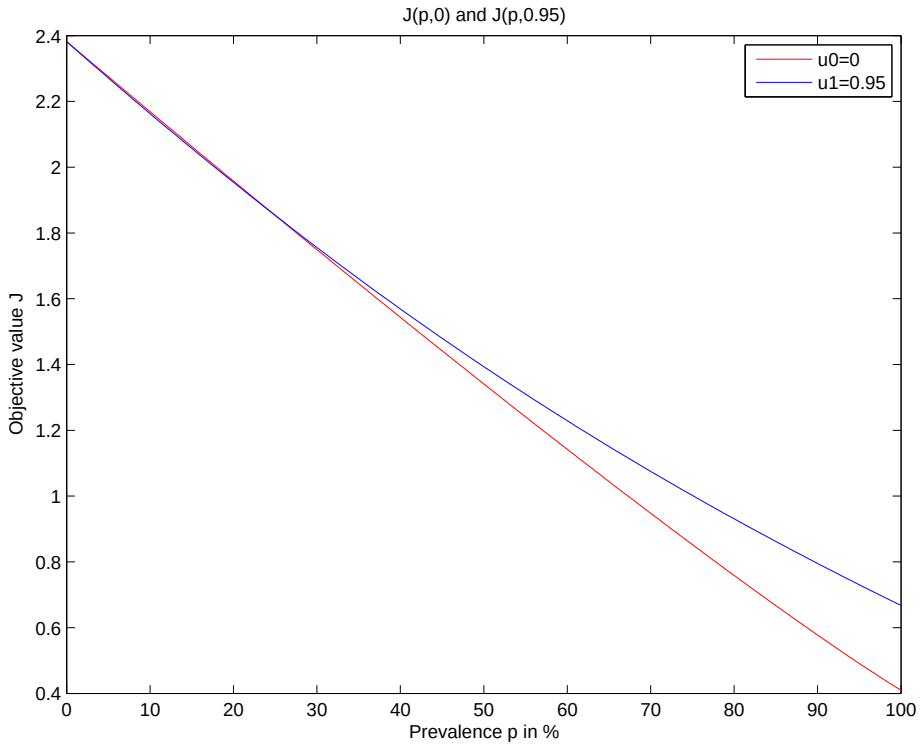

Figure 27: Threshold for $\sigma = 0.1$

Unlike as for CASE 2, we receive here a threshold already for a very low strength of the infection. The threshold occurs at a prevalence of about 23.67%, whereas the objective values for the two controls are very close, which means that their objective value is until a prevalence of about 30% very similar. Just as the results for CASE 1 and $\sigma = 0.1$, we receive curves for the controls, that are almost straight.

As a threshold occured for a strength of the infection of $\sigma = 0,1$ already, the next graphic is for $\sigma = 0.2$, to see how the threshold changes:

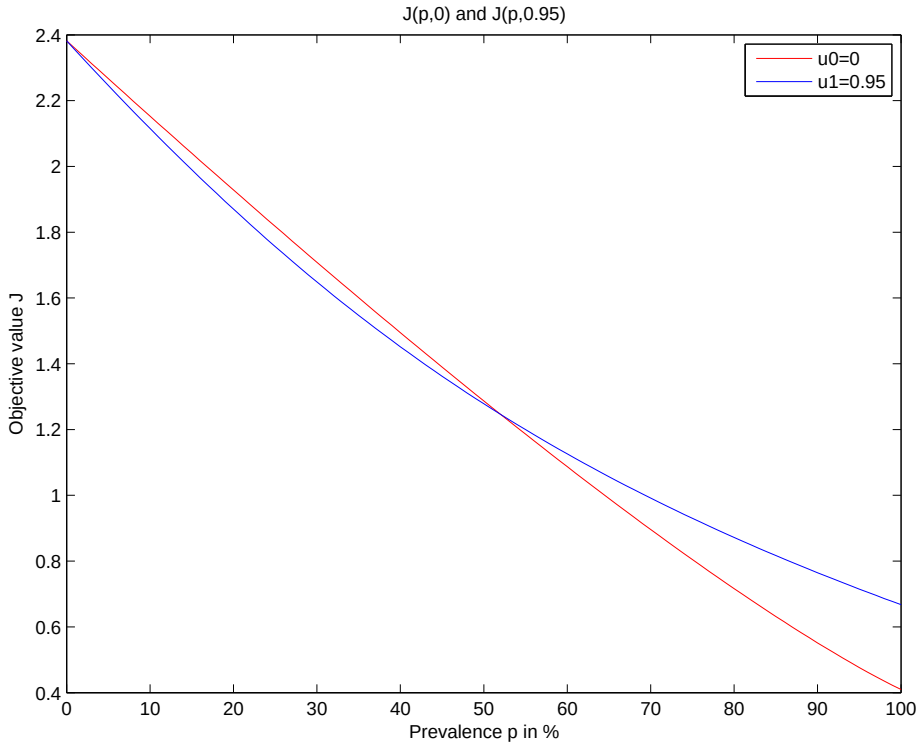

Figure 28: Threshold for $\sigma = 0.2$

The threshold now occurs at a prevalence of about 51.83%, so again, for a rather small variation of σ, the treshold moved more than 25% to the right. In comparison to CASE 1, where the threshold occured at a prevalence of about 15% for $\sigma = 0.2$, the threshold in CASE 2 is as well much more on the right side, which means that including the control variable in the objective function and for a greater β, the threshold moves much faster to the right for increasing σ. Again the curves for the two controls are quite close together, but not as much as for $\sigma = 0.1$. So for $\sigma = 0.2$ the objective values are as well rather close together until a prevalence of about 55%.

We already know that for $\sigma = 0.5$ the threshold occurs at a prevalence of about 61.33%, so now we have a look at the graphic for $\sigma = 0.6$, to see how the threshold changes for values close to 0.5:

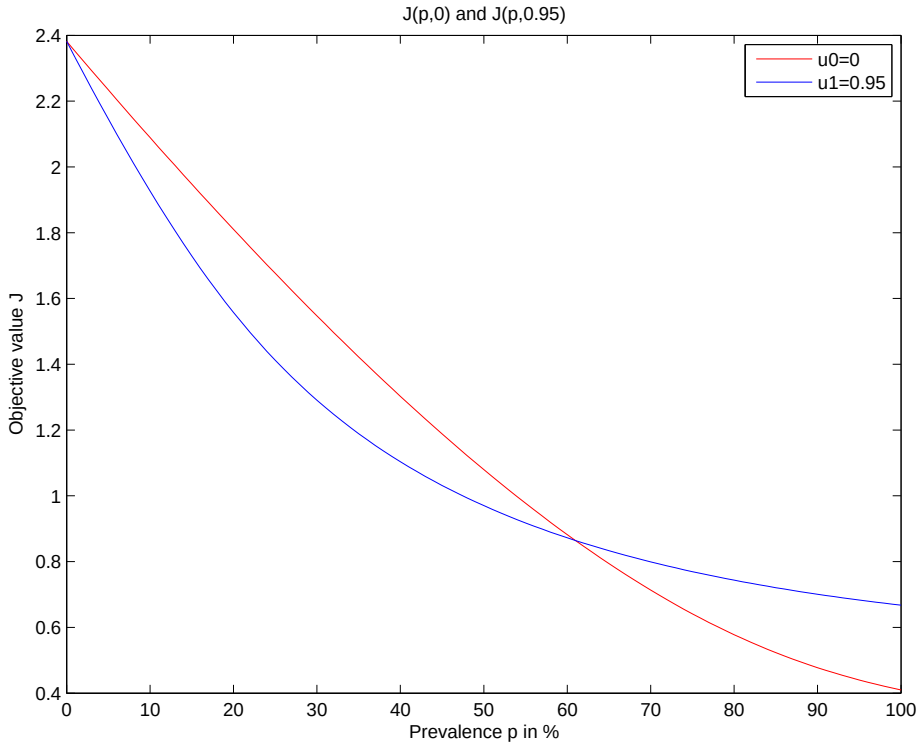

Figure 29: Threshold for $\sigma = 0.6$

Just like for CASE 1, the threshold here as well has not changed significantly compared to the results for $\sigma = 0.5$. Another investigation in comparison to CASE 1, is that here the slope of the curves is not that much decreasing as in Figure 24. So for this model and $\sigma = 0.6$ a higher prevalence does not lead to rather similar objective values as it does for high values in Figure 24.

Again, to sum up the main results of this section, we plot the threshold point in dependency on the strength of the infection for CASE 2:

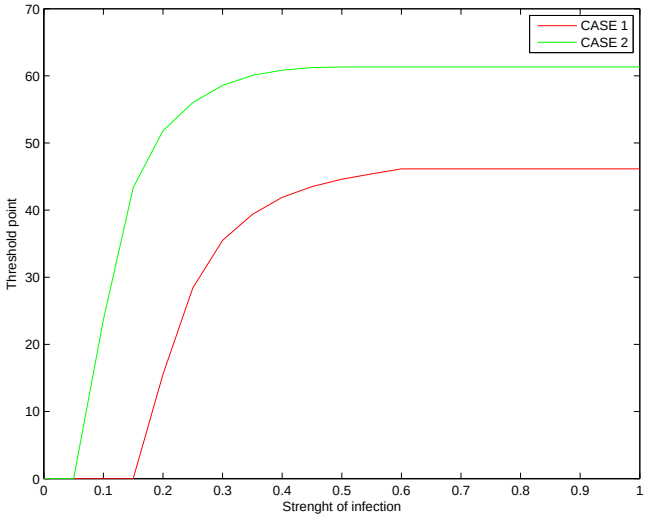

Figure 30: Threshold point depending on strength of infection σ

Just like as Figure 26 for CASE 1, we receive a curve, that is 0 at the beginning, has a strong increase afterwards and is almost equal to a certain prevalence until $\sigma = 1$. The main difference between this curve and Figure 26, is that here the threshold is already nonzero for a strength of infection higher than 0.06, so the strong increase occurs at a lower strength of infection than in CASE 1. Furthermore the threshold is almost similar for σ greater than 0.4 already. This means that we would have got quite similar results in section 4.1.2 in case of using a strength of the infection between 0.4 and 1. So the threshold in this model is not significantly dependent on the strength of the infection greater than 0.4.

Considering CASE 3

Finally, we consider the model with the parameters of CASE 3, which are mainly the same as in CASE 2, with the only difference that the constant in the objective function c is here equal to 0.4. Again the other parameters will be $\beta = 0.6$ (relative productivity of the infected individuals) $u_0 = 1$, $u_1 = 0.95$ (controls), $\mu = 0$, $r = 0.04$ and a constant mortality rate of the infected individuals dependent on infection time $\mu(\alpha) = 1$.

We already know that the threshold for $\sigma = 0.5$ occurs at a prevalence of about 80.56% for CASE 3.

For $\sigma = 0.1$ we receive:

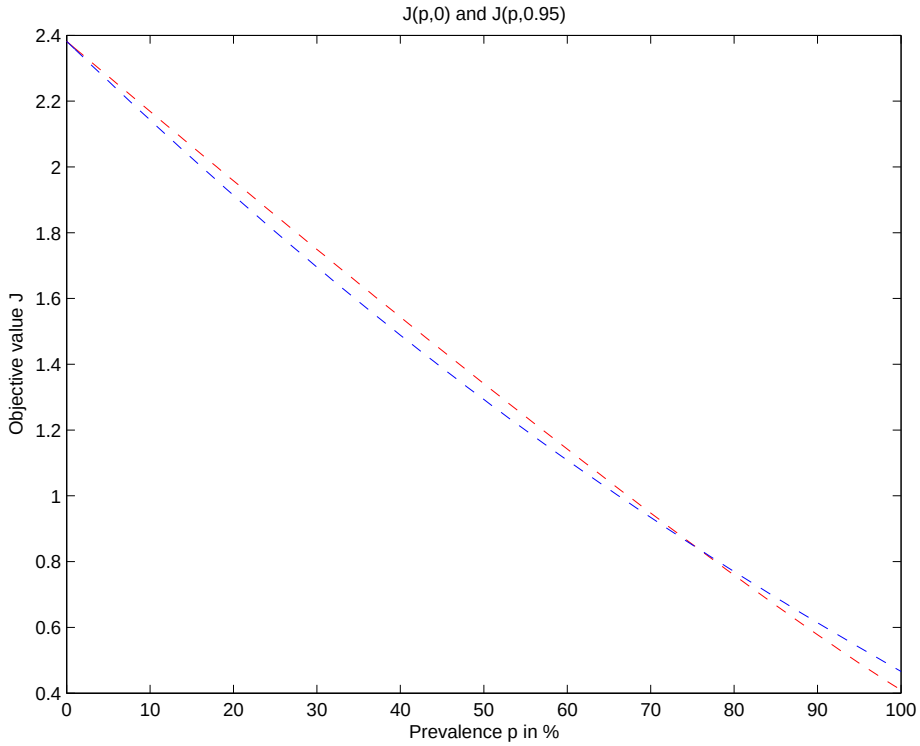

Figure 31: Threshold for $\sigma = 0.1$

In this case for a strength of infection of 0.1, a threshold occurs at a prevalence of about 75.54%. Therefore, in comparison to CASE 2, the treshold for $\sigma = 0.1$ occurs at a much higher prevalence (for CASE 2 at about 23.67%). Hence for a disease with an even very low strength of the infection, it is better to start treat the infected individuals just at a prevalence of more than 75.54%. In comparison to CASE 2 for $\sigma = 0.1$, this is a very low level, as in CASE 1, it was always better to treat the infected population for $\sigma = 0.1$. Furthermore the two curves for the controls are very close in this case, which means that the difference in the objective value between full medication and no medication is not very significant.

The next σ we consider is equal to 0.2, as our results for $\sigma = 0.1$ are already close to the threshold of our initial model for CASE 3 ($\sigma = 0.5$):

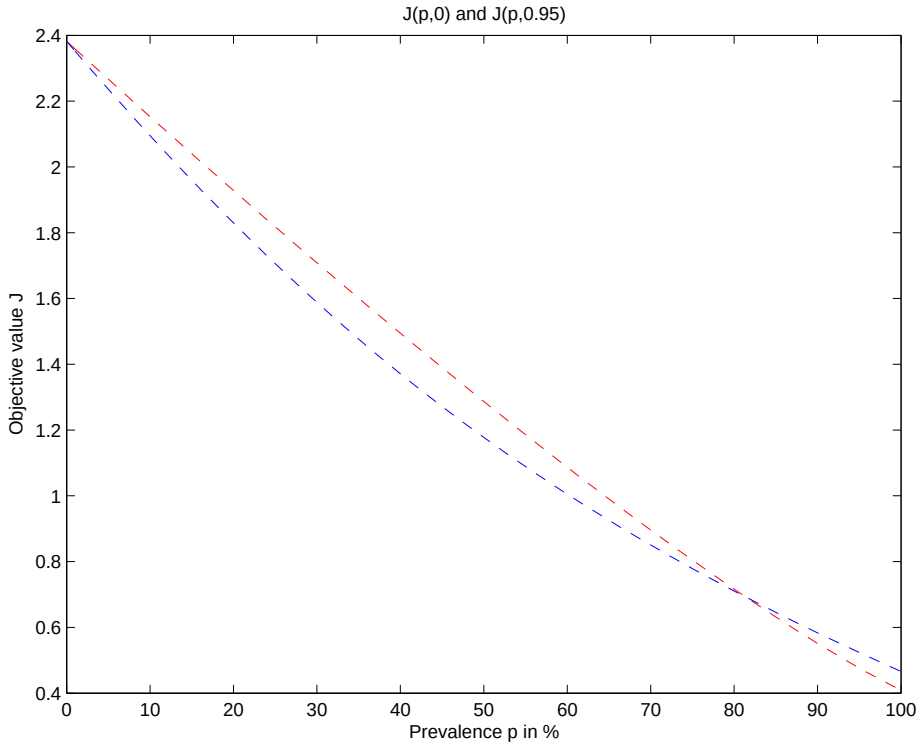

Figure 32: Threshold for $\sigma = 0.2$

The treshold moved to a prevelance of about 80.40%, so is already very close to our result for $\sigma = 0.5$. In comparison to the result for $\sigma = 0.1$, the curves for the controls are not as close together as before, therefore the especially until the threshold point, the difference between full medication and no medication is more significant than before.

As we already know from the previous two cases, the threshold is not moving very much after a certain σ. Here in this case, there is no threshold at $\sigma = 0$, and increases for $\sigma = 0.1$, but is already at a certain prevalence at $\sigma = 0.2$, that is very close to our initial results for $\sigma = 0.5$.

To confirm the assumption that the threshold is not increasing much more, we again plot the graphic for the treshold in dependency of the strength of the infection σ:

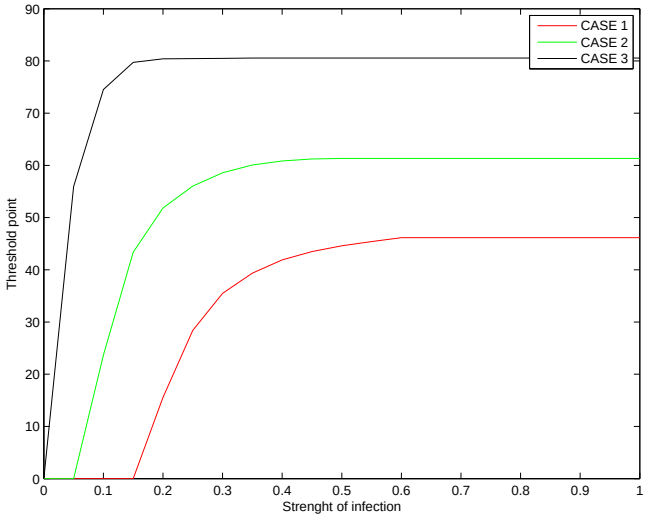

Figure 33: Threshold point depending on strength of infection σ

Thus here we see that just like as in the previous cases, the threshold is not varying significantly anymore after a certain point of the strength of infection σ. Compared to the other cases, there is no threshold just for $\sigma = 0$, afterwards the treshold is increasing until a prevalence of about 80%, and after $\sigma = 0.25$ not varying very much.

4.4 Overview of the Results

The main focus in this section was to investigate threshold points in the heterogenous model for different distribution functions, and to see how they change for different functions.

In section 4.1 we shown that for a homogeneous version of the model, there exist three different threshold points for the three different parametrizations considered. As a result of the use of three different cases, we investigated that the more the infected population is considered in the objective function and the higher the relative productivity β, the larger is the occuring threshold point.

In section 4.2 we introduced heterogeneity to the model by chosing different distribution functions. We investigated that for the three different cases the threshold moves to the right for a disease, which has an outbreak at the end of the time horizon and a smaller threshold for diseases which break out rather at the beginning of the time interval. Furthermore we were able to find a distribution function for one of the cases, so that the threshold point

is disappearing. In this special case it is always better not to medicate the infected population, but to let them die.

In the last section 4.3 we undertook a sensitivity analysis of the thresholds. Especially we considered an altering strength of the infection σ and how this is affecting the threshold point of the homogenous version of the model. For the three cases we investigated that for a higher strength of the infection age, the threshold point is moving to the right. Furthermore we found out that above a certain infectivity the threshold point is not altering significantly anymore. This occurs at a different amount of infectitivity for the different cases of parameters.

A Appendix

A.1 Solver

```
function [Y,P,Q] = age_primal_Christa(Y0,Nt,Np,Nq,h,funF,funG,...
                              funH,funPhi,U,V,PAR1,PAR2,PAR3);
%Solves the model from [F+T+V] with given controls U(ia,it),V(it),
%it = 1,...,Nt ,ia = 1,...Na, where Na is the number of columns of
%Y0. Everywhere the first dimension is the static dimenion of the
%vector, the second is age, the third is time.The function F must
%have the form Z = F(t,a0,ka,h,Yt,Pt,Qt,Ut,PAR1,PAR2,PAR3),
%where Z has dimension Ny x ka
%P = G(t,a0,b0,ka,kb,h,Yt,Ut,PAR1,PAR2,PAR3), with
%dim P = dim Np x ka x kb.
%Q = H(t,a0,ka,h,Yt,Pt,Ut,Vt,PAR1,PAR2,PAR3), with
%dim Q = Nq x ka.
%Y0 = Phi(t,Qt,Vt,PAR1,PAR1,PAR3), with dim Y0 = dim y (=Ny)
%Tested on 7.11.2001

min_L = 0;
[Ny,Na] = size(Y0);
Na1 = Na -1;
Y(:,:,1) = Y0;
P = zeros(Np,Na,Nt);
Q = zeros(Nq,Nt);
if (Np > 0)
   P(:,:,1) = integ2nm(h,feval(funG,0,0,0,Na,Na,h,Y(:,:,1),...
                    U(:,:,1),V(:,1),PAR1,PAR2,PAR3));
end
if (Nq > 0)
   Q(:,1) = integ2n(Na,h,feval(funH,0,0,Na,h,Y(:,:,1),...
                  P(:,:,1),U(:,:,1),V(:,1),PAR1,PAR2,PAR3));
end

Y(:,1,1) = feval(funPhi,0,Q(:,1),V(:,1),PAR1,PAR2,PAR3);

t = -h;
for (it1 = 2:Nt)
   t = t + h;
   t1 = t + h;
```

```
it = it1 - 1;
Yw(:,1) = feval(funPhi,t1,Q(:,it),V(:,it1),PAR1,PAR2,PAR3);
Yw(:,2:Na) = Y(:,1:Na1,it) + ...
  h*feval(funF,t,0,Na1,h,Y(:,1:Na1,it),P(:,1:Na1,it),...
           Q(:,it),U(:,1:Na1,it),V(:,it),PAR1,PAR2,PAR3);
if (Np > 0)
   P(:,:,it1) = integ2nm(h,feval(funG,t1,0,0,Na,Na,h,Yw,...
                      U(:,:,it1),V(:,it1),PAR1,PAR2,PAR3));
end
if (Nq > 0)
   Q(:,it1) = integ2n(Na,h,feval(funH,t1,0,Na,h,Yw,...
                     P(:,:,it1),U(:,:,it1),V(:,it1),PAR1,...
                     PAR2,PAR3));
end
Y(:,1,it1) = feval(funPhi,t1,Q(:,it1),V(:,it1),PAR1,PAR2,...
                    PAR3);
Y(:,2:Na,it1) = 0.5*(Yw(:,2:Na) + Y(:,1:Na1,it) + ...
   h*feval(funF,t1,h,Na1,h,Yw(:,2:Na),P(:,2:Na,it1),...
           Q(:,it1),U(:,2:Na,it1),V(:,it1),PAR1,PAR2,...
           PAR3));
```

A.2 Calculating the Objective Value for a Constant Distribution Function

This MATLAB-Code is for the calculation of the objective value dependent on a given prevalence and constant distribution function, we used in section 4.1 (representative for CASE 3).

```
function [Jobj]=Progcase6(contru,pt)

omega=300;
T=100;
h=0.1;
Na=floor(omega/h)+1;
Nt=floor(T/h)+1;
Np=0; Nq=2;

mu1=0;
mu2=1;
infect=ones(Na,1);
```

```
sigma=0.5;

U=contru*ones(2,Na,Nt);
U(2,:,:)=contru*ones(1,Na,Nt);
V=zeros(1,Nt);

PAR1(1)=T;
PAR1(2)=omega;
PAR1(3)=Nt;
PAR1(4)=Na;
PAR1(5)=h;
PAR1(6)=mu1;
PAR1(7)=mu2;
PAR1(8)=sigma;
PAR1(9)=pt;
PAR2=contru;
PAR3=infect';

function fct1=Function1(t,a0,ka,h,Yt,Pt,Qt,Ut,Vt,PAR1,PAR2,PAR3)
mu12=PAR1(6);
mu22=PAR1(7);
mu123=PAR1(6)*ones(1,PAR1(4)-1);
J=Qt(2,:);
I=Qt(1,:);
S=Qt(3,:);
sigma1=PAR1(8);
fct11=((-(mu12+(1-PAR2)*(mu22-mu12)))*Yt(1,:));
fct22=((-sigma1*J*S/(S+I))*ones(1,PAR1(4)-1)-mu123*S);
fct1=[fct11;fct22];
end

funF='Function1';

funG='NONE';

function fct2=Hfunction2(t,a0,ka,h,Yt,Pt,Ut,Vt,PAR1,PAR2,PAR3)
fct2(1,:)=Yt(1,:)/PAR1(2);
fct2(2,:)=Yt(2,:)/PAR1(2);
end
```

```
funH='Hfunction2';

function fct3=Phifunction3(t,Qt,Vt,PAR1,PAR2,PAR3)
J=Qt(2,:)
I=Qt(1,:);
S=Qt(3,:);
sigma1=PAR1(8);
fct31=(sigma1*J*S/(S+I));
fct32=(1-PAR1(9))/PAR1(2);
fct3=[fct31;fct32];
end

funPhi='Phifunction3';

Y0(1,:)=pt*ones(1,Na);
Y0(2,:)=(1-pt)*ones(1,Na);

[Ylsg,Plsg,Qlsg]=age_primal_Christa(Y0,Nt,Np,Nq,h,funF,funG,...
                            funH,funPhi,U,V,PAR1,PAR2,PAR3);

rinf=0.04;
betar=0.6;
c=0.4;

for t=1:1:Nt
S(t)=exp(-rinf*t)*(Qlsg(2,t)+(betar-c*contru)*Qlsg(1,t));
end

integ = integ2n(Nt,h,S);

Jobj=integ;
end
```

A.3 Plotting the Objective Value Dependent on the Prevalence for CASE 3

```
function out=findcritpnt4het(contru1,contru2)

schrittweite=0.01;
```

```
bestvalue1=zeros(1,101);

for t=1:1:101

bestvalue1(t)=Progcase6(contru1,(t-1)*schrittweite);

end

bestvalue2=zeros(1,101);

for t=1:1:101

bestvalue2(t)=Progcase6(contru2,(t-1)*schrittweite);

end

temp=0:1:100;

figure
plot(temp,bestvalue1(temp+1),'--r')
hold on
plot(temp,bestvalue2(temp+1),'--b')
hold off

title('J(p,0) and J(p,0.95)');
xlabel('Prevalence p in %');
ylabel('Objective value J');
h1leg=legend('u0=0','u1=0.95');
print -depsc Pic10.eps

end
```

A.4 Plot of Distribution Functions

A.4.1 Distribution Functions $I_0^1(\alpha)$ and $I_0^2(\alpha)$

```
omega=300;
x = 0:1:omega;
p=1;
y = (-(2*p)/omega)*(x-omega);
```

```
s = ((2*p)/omega)*x;

figure
g=area(y);
alpha(.7);
hold on
h=area(s);
alpha(.6);
hold off

set(g,'FaceColor',[0.5,0,0]);
set(h,'FaceColor',[0,0,0.5]);

title('Distribution Function I01(a) and I02(a) for p=1');
xlabel('time interval');
h1leg=legend('I01(a)','I02(a)');
print -depsc distrib12.eps
```

A.4.2 Distribution Function $I_0^3(\alpha)$

```
omega=300;
t= 0:1:omega;
p=1;

y1=zeros(1,omega+1);
for t=0:1:omega/3
    y1(t)=3*p-0.2;
end

y2=zeros(1,omega+1);
for t=omega/3+1:omega
    y2(t)=1/10;
end

t= 0:1:omega;

figure
area(y1)
hold on
area(y2)
hold off
```

```
title('Distribution Function I03(a) for p=1');
xlabel('time interval');
h1leg=legend('I03(a)');
print -depsc distrib3.eps
```

A.4.3 Distribution Functions $I_0^4(\alpha)$ and $I_0^5(\alpha)$

```
omega=300;
t= 0:1:omega;
p=1;

y1=zeros(1,omega+1);
for t=0:1:omega/5
    y1(t+1)=5*p;
end

y2=zeros(1,omega+1);
for t=4*omega/5:omega
    y2(t)=5*p;
end

t= 0:1:omega;

figure
g=area(y1)
hold on
h=area(y2)
hold off

set(g,'FaceColor',[0.5,0,0]);
set(h,'FaceColor',[0,0,0.5]);

title('Distribution Function I04(a) and I05(a) for p=1');
xlabel('time interval');
h1leg=legend('I04(a)','I05(a)');
print -depsc distrib45.eps
```

A.4.4 Distribution Functions $I_0^6(\alpha)$ and $I_0^7(\alpha)$

```
omega=300;
```

```
t= 0:1:omega;
p=1;

y1=zeros(1,omega+1);
for t=0:1:omega/10
    y1(t+1)=10*p;
end

y2=zeros(1,omega+1);
for t=9*omega/10:omega
    y2(t)=10*p;
end

t= 0:1:omega;

figure
g=area(y1)
hold on
h=area(y2)
hold off

set(g,'FaceColor',[0.5,0,0]);
set(h,'FaceColor',[0,0,0.5]);

title('Distribution Function I06(a) and I07(a) for p=1');
xlabel('time interval');
h1leg=legend('I06(a)','I0(a)');
print -depsc distrib67.eps
```

A.5 Threshold for Heterogeneous Models with Distribution Functions

For the calculations we used the same code as in A.2, with the only difference that instead of

```
Y0(1,:)=pt*ones(1,Na);
Y0(2,:)=(1-pt)*ones(1,Na);
```

which is the constant distribution function, we introduced the distribution functions.

A.5.1 Distribution Function $I_0^1(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
    Y0(1,alphacnt)=-(2*pt/omega)*(t1-omega);
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.2 Distribution Function $I_0^2(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
   Y0(1,alphacnt)=(2*pt/omega)*t1;
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.3 Distribution Function $I_0^3(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
if t1 <= (omega/3)
        Y0(1,alphacnt)=3*pt-0.2;
end
if t1 > (omega/3)
    Y0(1,alphacnt)=1/10;
end
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.4 Distribution Function $I_0^4(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
```

```
if t1 <= (omega/5)
        Y0(1,alphacnt)=5*pt;
end
if t1 > (omega/5)
    Y0(1,alphacnt)=0;
end
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.5 Distribution Function $I_0^5(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
if t1 >= (4*omega/5)
        Y0(1,alphacnt)=5*pt;
end
if t1 < (4*omega/5)
    Y0(1,alphacnt)=0;
end
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.6 Distribution Function $I_0^6(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
if t1 <= (omega/10)
        Y0(1,alphacnt)=10*pt;
end
if t1 > (omega/10)
    Y0(1,alphacnt)=0;
end
end

for alphacnt1=1:1:Na
```

```
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.7 Distribution Function $I_0^7(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
if t1 >= (9*omega/10)
        Y0(1,alphacnt)=10*pt;
end
if t1 < (9*omega/10)
    Y0(1,alphacnt)=0;
end
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

A.5.8 Distribution Function $I_0^8(\alpha)$

```
for alphacnt=1:1:Na
    t1=(alphacnt-1)*0.1;
if t1 >= (24*omega/25)
        Y0(1,alphacnt)=25*pt;
end
if t1 < (24*omega/25)
    Y0(1,alphacnt)=0;
end
end

for alphacnt1=1:1:Na
    Y0(2,alphacnt1)=1-pt;
end
```

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