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# Transmission-virulence trade-offs in vector-borne diseases

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**Abstract**

Though it is commonly supposed that there is a trade-off between virulence and transmission, there is little data and little insight into what it should look like. Here, we consider the specific case of vector-borne parasites (inspired by human malaria) and analyse an embedded model to understand how specific life-cycle aspects may affect this trade-off. First, we find that, for such parasites, the transmission function may have an S-shape. Second, we find that the trade-off obtained for vector-borne parasites is less sensitive to parameter variations than the trade-off obtained for directly transmitted parasites. Third, we find that other parasite traits, such as the conversion from replicative to infective stages, could have important epidemiological implications. Finally, we compare the effect of treatments targeting either the asexual or the sexual parasite life-stage.

*Key words:* within-host dynamics, epidemiology, virulence evolution, vector-borne diseases, trade-offs, *Plasmodium falciparum*, conversion rate, treatments, embedded models

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## 1 Introduction

2 Most models for the evolution of parasite virulence assume that it is governed  
by a trade-off between transmission and parasite-induced mortality (Ewald,  
4 1994). However, doubt has been cast on the universal validity of this basic  
assumption (Levin and Bull, 1994; Ebert and Bull, 2003). Though at some  
6 level there *should* be a relationship between parasite reproduction and nega-  
tive effects experienced by the host (otherwise we would hesitate to call the  
8 parasite a parasite), these negative effects are not necessarily expressed as ad-  
ditional mortality. Moreover, these negative effects, whatever they are, could  
10 depend on parasite exploitation and transmission strategies in a variety of  
ways (morbidity, anaemia, sterilisation).

12 Vector-borne parasites differ in a number of ways from the simple setting as-  
sumed in most models for the evolution of virulence. The most significant  
14 of these ways is that these parasites do not transmit through direct contact  
but require transmission via an intermediate host (the vector). Many para-  
16 sites fall into this category, including several protozoa such as *Plasmodium*  
parasites (the cause of malaria, see below) or *Leishmania*. Many of these par-  
18 asite infections are structured populations, where replication and transmission  
are carried out by different functional forms. There exists some support for  
20 a trade-off relationship between virulence and transmission in some vector-  
borne diseases (Mackinnon and Read, 1999b; Davies et al., 2001) but, as for  
22 most diseases (Lipsitch and Moxon, 1997), the evidence is scarce.

Several theoretical studies have explored vector-borne parasite virulence evo-  
24 lution. An argument based on a classical trade-off assumption predicts inter-

mediate or high virulence for vector-borne diseases. For instance, for indirectly  
26 transmitted parasites that use a mosquito to disperse, maintaining the main  
host in good health is less necessary (Ewald, 1983). Also, having a sexual life-  
28 stage could introduce a greater variability in virulence levels. Day (2002) uses  
an epidemiological model to study the importance of the contact rate (the rate  
30 at which a parasite gets a transmission opportunity). By assuming that this  
rate is constant for vector-borne diseases (because mosquitoes take care of the  
32 transmission), he shows that, under some conditions, Ewald's (1983) predic-  
tions are verified. Finally, Gandon (2004) developed a general framework to  
34 study multi-host parasites. He studies the case of vector-borne diseases and  
finds that differences in host immunisation could lead to higher levels of viru-  
36 lence (Gandon, 2004). Other models on vector-borne parasites usually involve  
malaria. Several models consider its within-host dynamics (for a review, see  
38 Molineaux and Dietz, 1999) but their purpose is usually to fit a given set of  
experimental data and typically they do not link within-host and epidemiolog-  
40 ical dynamics. To our knowledge, there have been no theoretical studies on the  
trade-off between transmission and virulence for malaria though studying the  
42 trade-off emergence for particular host parasite interactions might be crucial  
(Ebert and Bull, 2003).

44 In a previous study (Alizon and Van Baalen, 2005), we found that a trade-  
off relationship between transmission and virulence robustly emerges from  
46 within-host dynamics. We also found that although such trade-off curves tend  
to be convex, their precise shape depends sensitively on model parameters.  
48 This implies that the evolutionary stable level of virulence (ESV), *i.e.* the op-  
timal virulence, can strongly depend on the characteristics of the host-parasite  
50 interaction (*e.g.* life-cycle, parameter values). It also suggests that small phe-

notypical or genotypical variations among hosts and parasites are sufficient  
52 to blur the trade-off relationship. This model is a variation of the so-called  
‘embedded model’ approach, in which a model for within-host dynamics is  
54 combined with a larger-scale epidemiological model (for reviews, see Alizon  
and van Baalen, submitted; Mideo et al., submitted). Inspired by malaria, we  
56 therefore study an extension of our earlier model (Alizon and Van Baalen,  
2005) in which parasites alternate between two host species. We also assume  
58 that parasites are able to reproduce in both hosts, which means we are focus-  
ing on biological transmission (as opposed to mechanical transmission where  
60 the vector only carries the parasite). We will often refer to malaria for illustra-  
tive purposes, but several parasites species could fit this model (for instance  
62 protozoa such as *Leishmania*).

#### *About Plasmodium falciparum*

64 *Plasmodium falciparum* is one of the four species causing human malaria,  
which kills around 2 million people each year. Though it is a major cause  
66 of human death (3.1% of world mortality in 2002 was due to malaria, Anker  
and Schaaf, 2002), in the mortality sense malaria cannot be classified as a  
68 very virulent disease as most infected adults recover from the disease or sur-  
vive a relatively long time (Boyd, 1949). That is, the human host, at least  
70 the adults (children being much less immunised), does not seem to be an im-  
portant component among the factors that constrain malaria evolution. The  
72 majority of deaths caused by malaria seems to be due to a naive immune  
system (World Health Organization, 2003). This would explain why malaria  
74 mostly kills children from 6 months to 5 years, who are building their im-

munity, and foreigners, because their immune systems are not familiar with  
76 malaria (Carter and Mendis, 2002).

The parasite life cycle alternates between two host types: mosquitoes of the  
78 genus *Anopheles* and humans. An infected mosquito injects sporozoites when  
biting a human. This asexual form gives birth to merozoites that undergo  
80 clonal reproduction within the red blood cells (RBC) of the human host.  
Sometimes, infected RBCs produce sexual forms, called gametocytes (male or  
82 female). A mosquito that bites a human infected by *P. falciparum* may ingest  
some of these gametocytes. These ingested sexual stages may then, after going  
84 through a series of stages, settle in the salivary glands of the mosquito, which  
then becomes infective.

86 Experimental results suggest that a higher gametocyte density is linked with  
higher infectivity to mosquitoes (Taylor and Read, 1997; Mackinnon and Read,  
88 1999b; Drakeley et al., 1999; Schall, 2000). Gametocyte production is thus  
crucial to determining the parasite's reproductive success. Surprisingly, ga-  
90 metocytes only constitute a few percent of the circulating parasites (Eichner  
et al., 2001). Thus one may ask why gametocytogenesis is so slow (Taylor and  
92 Read, 1997; Mideo and Day, 2008).

## 2 The model

### 94 2.1 *Parasite Within-host Dynamics*

We first focus on the processes taking place inside the main host. This within-  
96 host model is derived from our previous model for persistent infections (Alizon

and Van Baalen, 2005). An important modification is that we distinguish two  
 98 within-host stages of parasites: a stage that can replicate within the host  
 (comparable to merozoites, the asexual stage of *Plasmodium*) and a stage  
 100 that can be transmitted (comparable to the gametocytes, the sexual life-stage  
 of *Plasmodium* which can be taken up by mosquitoes). Their densities are  
 102 respectively denoted  $x_1$  and  $x_2$ . Both life-stages are recognised and killed by  
 the same lymphocytes (with density  $y$ ) but with different successes, and while  
 104 the former reproduces asexually, only the latter can be transmitted. Koella and  
 Antia (1995) developed a similar model but for acute infections. The parasite  
 106 within-host dynamics are described by the following two equations

$$\begin{aligned} \frac{dx_1}{dt} &= (\varphi(1-m) - \sigma_1 y) x_1 \\ \frac{dx_2}{dt} &= \varphi m x_1 - \sigma_2 y x_2 \end{aligned} \tag{1}$$

where  $\varphi$  is the parasite intrinsic per capita growth rate,  $\sigma_1$  the killing rate of  
 108 asexual parasites by the immune system,  $\sigma_2$  the killing rate of sexual parasites  
 by the immune system and  $m$  the conversion rate of the parasites (*i.e.* for  
 110 malaria the proportion of RBC that develop into gametocytes). This set of  
 equations can be easily rendered dimensionless, however, in order to be able to  
 112 carry out our analysis, we will measure  $x_1$  and  $x_2$  in terms of absolute numbers  
 of parasites in the host. All the symbols used are summarised in Table 1.

114 Considering the specific case of malaria, one could expect gametocytes ( $x_2$ )  
 to be targeted by specific components of the immune system but empirical  
 116 evidence suggests that in fact they only suffer from cross-immunity with the  
 merozoites (for an overview, see Buckling and Read, 2001). Also, one might  
 118 ask why a framework for persistent infections can be applied to malaria. The

reason is that empirical evidence shows that *Plasmodium* infections can persist  
120 for several years, depending on the host and on the parasite species (Mack-  
innon and Read, 2004b). Old experimental data (Boyd, 1949) obtained on  
122 *Plasmodium vivax* also suggest that merozoite densities reach a stable state  
(of course such data is unavailable now because fortunately ethics rules ask  
124 for patients to be treated). Thus, we assume that the system reaches its equi-  
librium rapidly.

126 Finally, in this model we neglect multiple infections in order to keep the model  
tractable. This is of course an oversimplification and experimental data shows  
128 that co-infection dynamics in malaria can be highly complex (see *e.g.* de Roode  
et al., 2005; Råberg et al., 2006). Investigating the consequences of multiple  
130 infections on the evolution of *Plasmodium* will be the subject of a future study.

## 2.2 Modelling the Immune System

132 The strength of the immune response is represented by  $y$  and we assume that  
it is not constant but has a dynamics of its own. Following previous models  
134 reviewed in (Alizon and van Baalen, submitted), we assume that the dynamics  
of the lymphocyte clone (that carries out the immune response) is given by:

$$\frac{dy}{dt} = b + c_1 x_1 + c_2 x_2 - \delta y \quad (2)$$

136 where  $b$  is the base-line production rate of the lymphocytes,  $c_1$  the increase of  
lymphocyte production due to the asexual parasite,  $c_2$  the increase of lympho-  
138 cyte production due to the sexual parasite and  $\delta$  the lymphocyte mortality.

Here, we do not discriminate between the innate and acquired immune re-

140 sponse because we suppose the host never faces multiple infection (thus, both  
responses would be qualitatively similar in the model). The immune system  
142 is tremendously complex but simple ecological-like models can often account  
for much of this complexity (Anderson, 1994).

144 In this model, we do not introduce antigenic variation of the parasite. This  
aspect seems to explain why *P. falciparum* escapes the immune response and  
146 persists (Recker et al., 2004). Here we assume that persistence occurs and use  
a persistent infection framework.

### 148 2.3 Equilibrium densities

Within-host equilibrium densities can be found using equations (1) and (2):

$$\begin{aligned}\tilde{x}_1(\varphi, m) &= \frac{\sigma_2}{\sigma_1} \frac{(1-m)\delta\varphi - b\sigma_1}{c_2\sigma_1 m - (1-m)c_1\sigma_2} (1-m) \\ \tilde{x}_2(\varphi, m) &= \frac{(1-m)\delta\varphi - b\sigma_1}{c_2\sigma_1 m - (1-m)c_1\sigma_2} m \\ \tilde{y}(\varphi, m) &= \frac{1-m}{\sigma_1} \varphi\end{aligned}\tag{3}$$

150 One might ask why we defined a within-host system at all if we restrict our-  
selves to equilibrium situations. The main reason is that equation 1 and 2  
152 allow us to easily incorporate biological processes (parasite growth, conversion  
of asexual parasites into sexual parasites, destruction of the immune system).  
154 Without such a model, it would be impossible to assess how equilibrium den-  
sities should depend on the various parameters and variables. As underlined  
156 in (Alizon and Van Baalen, 2005), one of the main advantages of embedded

models is that instead of considering the host as a black box and one can study  
158 how changes in a given parameter affects parasite evolution. Even though HIV  
is not a vector-borne parasite, it provides a case in point because the density in  
160 the latent phase (when viraemia is low) is correlated with peak density in the  
acute phase Kelley et al. (2007). Unfortunately similar data is not available  
162 for vector-borne parasites.

## 2.4 *Epidemiological Dynamics*

### 164 *Parasite fitness*

To determine whether a parasite can invade a population, epidemiologists use  
166 the basic reproduction ratio ( $R_0$ ), *i.e.* the number of new infections caused by  
an infected host in a healthy population. A parasite can maintain itself in a  
168 host population if its  $R_0$  is greater than 1. Classically (Anderson and May,  
1991), if the transmission rate of a given micro-parasite is denoted  $\beta$ , the  
170 recovery rate  $\gamma$ , the natural host mortality  $\mu$ , the disease-induced mortality  
(or virulence)  $\alpha$  and the density of susceptible host  $S$ ,

$$R_0 = \frac{\beta}{\mu + \alpha + \gamma} S \tag{4}$$

172 For parasites that alternate between two hosts, the parasite's overall  $R_0$  in-  
volves the two hosts. The strict alternation of the parasite's two hosts implies  
174 that their contributions are in series and can be decoupled (Anderson and  
May, 1991; Heffernan et al., 2005). If the  $v$  suffix refers to the vector and the  
176  $h$  suffix to humans, we get

$$R_0 = \frac{\beta_{v \rightarrow h}}{\mu_v + \alpha_v + \gamma_v} S_v \cdot \frac{\beta_{h \rightarrow v}}{\mu_h + \alpha_h + \gamma_h} S_h \quad (5)$$

Here, we assume that the epidemiological parameters (virulence, transmission  
 178 and recovery) in the vector are constant. This implies that the vector com-  
 ponent of the  $R_0$  is constant. All these assumptions are of course debatable  
 180 but there is some support in the literature (see *e.g.* Ferguson et al., 2003). We  
 also implicitly assume that the density of the vector population reaches its  
 182 equilibrium more rapidly than the human population density, *i.e.* that  $S_v$  is  
 constant.

184 Thus, the expression of the parasite's  $R_0$  becomes

$$R_0 \propto \frac{\beta_{h \rightarrow v}}{\mu_h + \alpha_h + \nu_h} S_h \quad (6)$$

Following the approach adopted in previous studies of embedded models (re-  
 186 viewed in Alizon and van Baalen, submitted; Mideo et al., submitted) we then  
 link the parasite within-host dynamics to the epidemiological parameters of  
 188 the main host (transmission and virulence).

### *Parasite transmission rate*

190 Here, the force of the infection of the vector population (*i.e.* the risk for a  
 human to become infected after being bitten by a mosquito) depends on the  
 192 efficiency of transmission from humans to vector. As in Koella and Antia  
 (1995) and following experimental data described in the Introduction, we link  
 194 the equilibrium density of sexual parasites ( $\tilde{x}_2$ ) and transmission from the  
 main host to the vector ( $\beta_{h \rightarrow v}$ ).

196 Theoretically, in the case of sexual vector-borne parasite, two sexual para-  
 sites (one of each sex) are enough to infect the vector. However, following  
 198 the evidence that there is a strong immune response within the mosquito  
 (Dimopoulos, 2003), we assume that a minimum number of sexual parasites  
 200 within the blood meal is required to overwhelm the mosquito’s immune system  
 and successfully infect it.

202 A mosquito ingests approximately 1 to 4  $\mu\text{L}$  during a blood meal (Jeffery, 1956)  
 and there are approximately 5L of blood in the human body. If  $M$  is the mean  
 204 number of sexual parasites within 4  $\mu\text{L}$  of blood (*i.e.*  $M = 8.10^{-7} \tilde{x}_2$ ), then  
 the probability  $p_n(M)$  of having exactly  $n$  sexual parasites in the mosquito  
 206 blood meal is Poisson-distributed:

$$p_n(M) = \frac{M^n e^{-M}}{n!} \quad (7)$$

Thus, we can define the transmission rate  $\beta_{h \rightarrow v}(\varphi, m)$  as

$$\beta_{h \rightarrow v}(\varphi, m) = a P_n(\tilde{x}_2(\varphi, m) \cdot 8.10^{-7}) \quad (8)$$

208 where  $a$  is a transmission constant and  $P_n$  is the probability of having at least  
 $n$  sexual parasites in a given volume of blood. More precisely,

$$P_n(M) = 1 - \sum_{i=0}^{n-1} \frac{M^i e^{-M}}{i!} \quad (9)$$

210 Assessing the number of sexual parasites required to establish an infection  
 ( $n$ ) is not simple. Here, for numerical calculations, we arbitrarily take  $n = 40$   
 212 because for malaria it is the gametocyte detection density in 4  $\mu\text{L}$  (a mosquito  
 blood meal). For further details on the effect of  $n$  on our results, see Appendix  
 214 A.

### *Parasite virulence*

216 Parasite virulence is notoriously difficult to define. Here, we assume that the  
negative effects experienced by the host are proportional to the overall repli-  
218 cation rate of the asexual parasites ( $\varphi \tilde{x}_1$ ). However, sexual parasites could  
potentially also have deleterious effects as could (corroborated by an increas-  
220 ing amount of evidence) the immune system itself through immunopathology  
phenomena (Kwiatkowski, 1991; Graham et al., 2005). Assuming all negative  
222 effects express themselves as increases in the mortality rate, we assume that  
virulence is given by

$$\alpha(\varphi, m) = u_1 \varphi \tilde{x}_1(\varphi, m) + u_2 \tilde{x}_2(\varphi, m) + w \tilde{y}(\varphi, m) \quad (10)$$

224 The main contribution to parasite virulence comes from the asexual life-stage  
because sexual parasites do not replicate. Note that according to this equa-  
226 tion the cost of a strong immune response (represented by the third term in  
equation 10) may be well offset by the advantage associated with a reduced  
228 parasite density (the first and second terms).

There are other ways of defining a virulence function (Alizon and Van Baalen,  
230 2005), *e.g.* without immunopathology ( $w = 0$ ) or without the overall replica-  
tion rate (using  $\tilde{x}_1$  instead of  $\varphi \tilde{x}_1$ ). With the transmission function we use,  
232 all these definitions lead to qualitatively similar results.

Incorporating the transmission process and the virulence mechanisms into  
234 equation 6, we obtain the following expression for the  $R_0$  as a function of  
within-host processes

$$R_0(\varphi, m) \propto \frac{a P_n(8.10^{-7} \tilde{x}_2(\varphi, m))}{\mu_h + u_1 \varphi \tilde{x}_1(\varphi, m) + u_2 \tilde{x}_2(\varphi, m) + w \tilde{y}(\varphi, m)} S_h \quad (11)$$

236 where the equilibrium values are given by equation 3.

We analyse how the parasite's  $R_0$  depends on its within-host growth rate  $\varphi$   
238 and its conversion rate  $m$ . Unfortunately, this function is too complex for a  
complete analysis but we still can develop a numerical ESS analysis.

240 Table 1 here

### 3 Results

#### 242 3.1 An S-shaped Transmission Function

We find that the transmission rate (equation 8) has an S-shape both when it is  
244 considered as a function of the growth rate  $\varphi$  or as a function of the conversion  
rate  $m$  (figure 1). This shape results from the stochasticity associated with  
246 the transmission process. The value of the infective threshold (in terms of the  
number of sexual parasites) necessary to launch an infection in the mosquito  
248 affects the  $\varphi$  value for which the saturation occurs.

figure 1 here

250 Note that an S-shaped transmission curve implies a positive density depen-  
dence at low densities together with a negative density dependence at high  
252 densities. This creates an infection threshold (see also Regoes et al., 2002).

### 3.2 Emergence of a Trade-off Between Transmission and Virulence

254 We plot the parametric curve  $(\mu + \alpha(\varphi), \beta(\varphi))$  which depends on the parasite  
growth rate  $\varphi$  (figure 2A) and  $R_0(\varphi)$  (figure 2B) for a given set of parame-  
256 ter values. The dot indicates the evolutionary stable virulence (ESV) value,  
*i.e.* the virulence for which the fitness of the parasite (given by equation 11)  
258 is maximised. For low levels of virulence, transmission accelerates with viru-  
lence but it quickly levels of to a plateau value. Near the ESV the curve is  
260 strongly convex (figure 2A), which implies that here, contrary to our previous  
approach with a linear transmission function (Alizon and Van Baalen, 2005),  
262 small variations of  $\varphi$  may have an important effect on the  $R_0$  value of the  
parasite (figure 2B).

264 This can be seen in figure 2B: the peak of the  $R_0$  function at the optimal  
parasite growth rate is thinner with the sigmoid transmission function (plain  
266 curve) than with the linear transmission function (dashed curve). Thus, the  
cost of expressing a virulence higher or lower than the optimum is huge.

268

figure 2 here

### 3.3 Parameter Influence on the Optimal Virulence

270 Compared to the standard case of a linear transmission function, the optimum  
less sensitive to changes in parameter values. For a given set of parameters,  
272 we can determine the evolutionary equilibrium (*i.e.* the optimal growth rate  
 $\varphi^*$  maximising  $R_0$ ). This optimum can also be indicated by giving the opti-  
274 mal virulence and the optimal transmission ( $\alpha(\varphi^*)$  and  $\beta(\varphi^*)$ ) which is the

intersection of the curve and the tangent that passes through the origin of  
276 the graph (Van Baalen and Sabelis, 1995a). By changing a parameter, we can  
follow the variation of the evolutionary optimum.

278 figure 3 here

Figure 3 presents a sensitivity analysis for the host natural mortality rate ( $\mu$ )  
280 for a case with a linear transmission function and for a case with an S-shaped  
transmission function. Comparison of the two figures suggests that the optimal  
282 level of virulence is much more stable if the transmission function saturates.

We find that variation of many parameters, most notably of those linked to  
284 the parasite (such as  $m$  or  $\sigma_1$ ) have very little effect on the optimal virulence  
(for a comparison with linear transmission, see Alizon and Van Baalen, 2005).  
286 Thus, parameter variation may not strongly affect the selection pressure.

### 3.4 *The Optimal conversion rate*

288 In addition to having to ‘choose’ an optimal growth rate, the parasite has to  
trade off replication (through asexual parasites) and transmission (through  
290 sexual parasites) in its main host. In other words, it has to optimise its con-  
version rate from host resources into transmitted propagules.

292 figure 4 here

When the parasite’s reproductive success ( $R_0$ ) is plotted as a function of  $m$   
294 and  $\phi$  (figure 4), we observe that if the parasite growth rate is high enough

( $\varphi \geq 0.1$ ), there are two locally optimal strategies for the parasite: one with  
296 a high conversion rate ( $m \geq 0.8$ ) and another with a low conversion rate  
( $m \leq 0.1$ ). This bistability comes from the fact that two combinations of  
298  $m$  and  $\varphi$  allow to produce the same number of sexual parasites. Note that  
when the growth rate is too high ( $\varphi > 0.8$ ), only the strategy with a high  
300 maturation rate is viable. The reason is that low conversion rates lead to high  
burden of asexual parasites which have a strong effect on virulence. We discuss  
302 the implications of these results in the Discussion.

If sexual parasites do not contribute to virulence (*i.e.*  $u_2 = 0$ ), then there is a  
304 unique optimal strategy: the strategy with high conversion rates (Appendix B).  
This makes sense because if sexual parasites are harmless and less targeted by  
306 the immune system, rapid conversion is a ‘refuge’ strategy (parasites colonise  
a niche without predators).

308 If we choose a linear transmission function, the parasite’s  $R_0$  is maximised  
for a unique conversion value. However, the shape of the  $R_0$  curve may vary.  
310 Without sexual parasites contributing to virulence, the optimal conversion rate  
is clearly defined by a unique peak of the  $R_0$  function. In contrast, if sexual  
312 parasites have an effect, the peak flattens to become a plateau which means the  
optimal conversion strategy is more sensitive to variations in parameter values  
314 (see Appendix C for further details). Thus, independently from the shape of  
the transmission function, our results suggest that the optimal conversion  
316 strategy will depend on the detrimental effects of clonal and sexual life-stages.

### 3.5 Consequences of Health Policies

318 Anti-parasite treatments are known to influence parasite resistance but some  
suggest they might affect other parasite life-history traits such as virulence as  
320 well (Gandon et al., 2001). Treatments may act in different ways and this can  
lead to very different evolutionary outcomes (Gandon et al., 2001; Alizon and  
322 Van Baalen, 2005; André and Gandon, 2006). Here, we study the evolutionary  
consequences of treatment strategies that differ in the parasite life-stage they  
324 target. In the first case, the treatment targets clonal life-stages (merozoites)  
and we add an extra mortality term ( $\tau_1$ ) to  $x_1$ . In the second case, the treat-  
326 ment targets sexual life-stages and we add an extra mortality term ( $\tau_2$ ) to  $x_2$ .  
Equation 1 is now

$$\begin{aligned}\frac{dx_1}{dt} &= (\varphi(1 - m) - \sigma_1 y - \tau_1) x_1 \\ \frac{dx_2}{dt} &= m \varphi x_1 - (\sigma_2 y + \tau_2) x_2\end{aligned}\tag{12}$$

328 where  $\tau_1$  and  $\tau_2$  are the intensities of the treatment.

In the short term, both these treatments reduce disease-induced mortality  
330 by decreasing parasite load. Not surprisingly, increasing the intensity of the  
treatment reduces the parasite's  $R_0$  (figure 5). The treatment against the  
332 clonal parasite (*i.e.* increasing  $\tau_1$ ) is not very efficient at reducing the  $R_0$ . In  
contrast, targeting the sexual parasite (*i.e.* increasing  $\tau_2$ ) has a clear impact  
334 on the parasite's fitness.

figure 5 here

336 To study the evolutionary consequences of treatment strategies, we assess  
how the parasite's within-host growth rate evolves in response to a particular  
338 treatment effect. As we have argued, this parasite within-host growth rate is  
a better measure than host mortality as growth rate is positively correlated  
340 with the harmfulness of the parasite whereas host mortality (*i.e.* virulence)  
is itself a compound parameter that only reveals the result of the interaction  
342 between the parasite and the host. We find that parasites can always survive  
a treatment targeting the asexual life-stage by evolving towards growth rates  
344 high enough to ensure a  $R_0$  greater than 1 (figure 5A). For a treatment tar-  
geting the sexual parasite (figure 5B), increasing the growth rate may not be  
346 sufficient for the parasite to restore its  $R_0$ . It is important to note that treat-  
ments also affect the optimal conversion rate. For instance, extra-mortality of  
348 the asexual life-stage parasites may select for lower conversion rates, which  
partially counteracts the effectiveness of the treatment (figure not shown).

350 Other types of anti-parasite treatments can be studied by varying parame-  
ter values (Alizon and Van Baalen, 2005). For instance, an anti-growth rate  
352 treatment that decreases  $\varphi$  would be very similar to a treatment targeting  
gametocytes only.

## 354 4 Discussion

Several studies have tried to work out from first principles the possible shapes  
356 of the trade-off between transmission and virulence (Alizon and van Baalen,  
submitted; Mideo et al., submitted). This study attempts to test the general  
358 theory of trade-off evolution by assessing how well it can be applied to a  
more specific case. Ganusov and Antia (2003) previously studied the effect of

360 variations in the virulence and transmission functions. Though they modelled  
acute infections they did not link these variations to specific diseases. Gilchrist  
362 and Coombs (2006) also developed a general embedded model to study how  
the concavity of transmission and virulence functions affect the evolution of  
364 viruses that compete for within-host resources.

Here, we study the case of vector-borne parasites using the malaria parasite *P.*  
366 *falciparum* as an illustrative example. We incorporate several aspects of these  
parasites in our model. Thus, in our model (1) parasites alternate between two  
368 types of hosts, main host and vector, (2) within the main host, replication and  
transmission are carried out by functionally different forms, and (3) parasites  
370 also reproduce within the vector (no passive transmission). We studied the  
effects of these mechanisms by working out how they modify the relationship  
372 between transmission and virulence relative to the standard case of direct  
transmission (Alizon and Van Baalen, 2005). We briefly summarise the main  
374 implications here and discuss the perspectives of our study.

#### 4.1 *Transmission*

376 Virulence is assumed to be governed by a trade-off with transmission but the  
process of transmission itself may influence virulence evolution in more than  
378 one way (Day, 2001; Regoes et al., 2002). An important consequence of the  
fact that a parasite requires mosquitos as vectors, is that the infectivity of  
380 a patient is not simply proportional to the density of sexual parasites that  
circulate in its blood. For instance, in the case of malaria, a mosquito can  
382 only effectively convert a limited number of gametocytes into sporozoites;  
additional gametocytes ingested by a mosquito are thus essentially wasted.

384 Stochasticity in the number of parasites ingested by a mosquito may give rise  
to an accelerating relationship between density and infection success for low  
386 densities of sexual parasites. In other words, when a mosquito bites a human,  
it may not ingest enough sexual parasites to become infected. An S-shaped  
388 transmission function, as assumed in some theoretical studies (Regoes et al.,  
2002), then emerges quite naturally from the underlying biological mecha-  
390 nisms.

Recently, Paul et al. (2007) showed experimentally that there exists a thresh-  
392 old gametocyte density above which mosquito infection rates considerably  
increase. They also showed that for high gametocyte densities, mosquito in-  
394 fection rates level off. These two results corroborate the main features of our  
model.

#### 396 4.2 *A fixed value of optimal virulence*

When the particular aspects of a vector-borne parasite are taken into account,  
398 a saturating trade-off results which yields a very robust evolutionary stable  
virulence (ESV) value. The precise mathematical definition of the virulence  
400 function has little effect on the existence of an ESV and the ESV value is less  
sensitive to parameter variation than a value obtained with a linear trans-  
402 mission function (Alizon and Van Baalen, 2005). An interesting consequence  
is that when the transmission function levels off, high levels of virulence are  
404 never predicted. This could explain low levels of virulence observed for some  
vector-borne disease like malaria in its adult human host: as after a given  
406 threshold increasing parasite density only increases virulence, very virulent  
strains are strongly counter-selected.

408 We also find that the constants relating to deleterious effects ( $u$  and  $w$ ) may  
have a strong effect on ESV values, making it difficult to predict biological  
410 values. However, we find that when the transmission function is S-shaped,  
host natural mortality ( $\mu$ ) has very little effect on the ESV. This implies that  
412 to better calibrate these models to malaria we ‘only’ need to get insight on  
biological values of gametocyte and merozoite deleterious effect. In contrast, in  
414 models with a linear transmission rate, *both* natural mortality and deleterious  
effect constants have strong effect on the ESV. Our study helps to identify  
416 the problems and potential shortcomings of trade-off theory when trying to  
predict optimal levels of virulence for specific cases.

#### 418 *4.3 Maturation or Growth?*

Our study highlights the fundamental incompatibility of conversion and growth.  
420 One may find two distinct and locally stable equilibria with similar reproduc-  
tive success: in the first case parasites specialise in the production of asexual  
422 parasites (low conversion rate) while in the second parasites specialise in the  
production of sexual parasites (high conversion rate). This dilemma resembles  
424 the trade-off between transmission and virulence: a lower conversion rate leads  
to less transmission, but to a longer infectious period (because it is less easy  
426 for the immune system to clear the clonal life-stage).

In the case of human malaria, many studies have tried to understand why  
428 the conversion rate is so low. Taylor and Read (1997) suggest two evolution-  
ary explanations: either high gametocyte densities in a blood meal lead to  
430 oocyst burdens that are so high that it would kill the mosquito or the immune  
response targeting the gametocytes is density dependent. It is interesting to

432 note that there is also a plastic variability in conversion rates. For instance,  
experimental studies show that conversion occurs more rapidly in immunised  
434 or treated hosts (Dyer and Day, 2000). This suggests that the optimal con-  
version rate might depend on specific events, *e.g.* the occurrence of multiple  
436 infections.

The best way to understand the optimal conversion rate is perhaps to interpret  
438 this problem in terms of optimal foraging: the parasite has to choose between  
local growth or high dispersal. A parasite with a high conversion rate is easily  
440 outcompeted locally, which is often a problem given the high frequency of  
multiple infections (Read and Taylor, 2001). Thus, multiple infections could  
442 also act on the optimal conversion rate by favouring low maturation rate.

Mideo and Day (2008) reach a similar conclusion by using an epidemiological  
444 approach. They find a similar bistable equilibrium state (with either high or  
low conversion rates) but without assuming any virulence in the main host.  
446 They show that introducing superinfections favours the low conversion rate  
equilibrium. A further step would be to study an embedded model which takes  
448 multiple infections into account.

#### 4.4 *Which Life-stage to Target?*

450 It has been shown recently that serial passages of *Plasmodium chabaudi* in  
immune mice select for increased levels of virulence (Mackinnon and Read,  
452 2004a). Of course, in a serial passage experiment, transmission stages have  
very little importance in their experiment and it is the ability to colonise  
454 a host which is selected for. It is thus possible that parasites may increase

their growth rates because their transmission does not level out anymore.  
456 Nevertheless, this experiment tends to confirm two of our results: treatment  
may select for higher levels of virulence and bypassing transmission stages  
458 might select for even higher levels of virulence.

More precisely, we find that treatments targeting the sexual part of the par-  
460 asite's life-cycle are the most efficient: not only do they greatly reduce the  
parasite's  $R_0$ , but also they make it very difficult for the parasite to escape  
462 eradication. Thus, at an individual level, a host should destroy clonal life-  
stages to reduce its own mortality. In contrast, at a population level, hosts  
464 should target sexual parasites instead to reduce the parasite's reproductive  
success. Thus, there is a conflict between the optimum of the individual and  
466 that of the population, as noticed by several authors (Anderson and May,  
1991; Van Baalen, 1998; Alizon and Van Baalen, 2005).

468 Our results raise some interesting points with respect to treatments targeting  
the transmission stages. In contrast to the study by Gandon et al. (2001),  
470 our model does not predict that transmission-blocking treatments will select  
for lower levels of virulence. There are two reasons for this. The first is that  
472 Gandon et al.'s prediction hinges upon the occurrence of superinfection which  
is not included in our model (Van Baalen and Sabelis, 1995b; Alizon and  
474 Van Baalen, 2005). The second reason is that actively destroying transmission  
stages is not the same as 'blocking transmission'. In the former case, the treat-  
476 ment can be counteracted by the parasite whereas in the latter the treatment  
does not affect the parasite optimum and it is only through an epidemiological  
478 feedback loop (for instance through multiple infections) that anti-transmission  
treatment may influence parasite virulence evolution.

480 Ironically, deciding which anti-parasite therapies to use might lead to a similar  
dilemma. One may develop an anti-transmission life-stage treatment, which  
482 may be very efficient at getting rid of the parasite but which might select for  
more virulent parasites if the eradication fails. To avoid this, one can develop  
484 an anti-growth rate treatment (targeting the clonal life-stage) which is also less  
likely to select for highly virulent strains but which is less likely to eradicate  
486 the parasite. This suggest that there may be a conflict between the short-  
term objectives of therapies and their long-term consequences. Of course on  
488 the short term the priority is to heal infected people, which means decreasing  
their parasitaemia by using treatments targeting merozoites. The problem is  
490 that this public health strategy is very unlikely to eradicate the parasite at  
a population level. A solution could be to couple short term treatments of  
492 infected hosts with preventive vaccination against gametocytes.

## Conclusions

494 Our model is designed to study the evolution of the trade-off between trans-  
mission and virulence but it reveals other interesting aspects of parasite evo-  
496 lution. In particular, it underscores the importance of the choice the parasite  
has to make between local competition or dispersal (for another example, see  
498 Gandon, 1998). How these components interact with sexual selection, known  
to be important in *Plasmodium* for instance, is as yet an open question. Also,  
500 we find that for vector-borne parasites with different life-stages, treatments  
might have different evolutionary consequences depending on the life-stage  
502 they target.

Unfortunately, realism had to be sacrificed to keep our model tractable. This

504 makes some conclusions difficult to apply to specific cases. For instance, we  
do not model in detail the complex oscillating behaviour of merozoite and  
506 gametocyte densities that occur in patients infected with malaria. Neither  
do we incorporate heterogeneity in the host population which could be very  
508 important. For malaria, for instance, children are supposed to be an important  
gametocyte reservoir (Van der Kolk et al., 2003). Thus, precise application of  
510 our results, for instance to malaria, might require some more complexity.

Our model indirectly addresses the question of malaria's low virulence by  
512 suggesting that virulence evolution could be driven mainly by the transmission  
function. However, we must add that several other factors have been proposed  
514 to explain this matter. It may be that mortality is not appropriate at all as a  
virulence measure for *P. falciparum* infections and that sub-lethal effects, like  
516 weight loss, should be considered (Mackinnon and Read, 1999a; Paul et al.,  
2004). This is just another way to state that in malaria infections there is  
518 no clear trade-off between transmission and host death rate. However, the  
sigmoid constraint function that emerges from our model leads to the same  
520 prediction: virulence is low with little effect on transmission. Thus, contrary  
to the view that trade-offs do not exist (Ebert and Bull, 2003), our study  
522 highlights that they do exist but that their properties may be unexpected. A  
next step towards resolving this issue is to consider a model that, in contrast  
524 to the one we studied here, also explicitly accounts for the possible sub-lethal  
effects. Another hypothesis to explore is host developmental heterogeneity: it  
526 might be that malaria virulence is 'hidden' in adults because of a very strong  
immune system. In this case, child mortality would be the proper indicator of  
528 malaria virulence as young children are not immunised.

Finally, many authors argue that multiple infections are essential to under-

stand parasite virulence (Van Baalen and Sabelis, 1995a; Read and Taylor, 2001; Brown et al., 2002). For malaria for instance, infections by several *Plasmodium* species (Zimmerman et al., 2004) or by several clones (Day et al., 1992) are common. A possible consequence is that a host might be able to recover from one infection but not from many simultaneous infections: even if each parasite has a low virulence, the total virulence can be high. Multiple infections modify the selection pressure at several steps of the parasite's life-cycle: there will be competition between the different genotypes to have sexual parasites in the mosquito's blood meal, there will be competition within the mosquito to gain access to the salivary glands and there may be resource competition within the main host. This competition will affect both growth rate and the conversion rate because the parasite strain with the highest net growth rate (growth rate times proportion of parasites that do not mature) is likely to overwhelm the others. Considering multiple infections could also be a means to introduce reproduction between different parasite genotypes (within the mosquito) which would create parasite diversity. This could be crucial to understand how this parasite evades the immune system.

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**A Effect of the threshold sexual stages density value ( $n$ )**

554 In this study, we choose  $n = 40$  to calibrate our model with the malaria case.  
However, the precise value of  $n$  (the number of sexual parasites required to  
556 successfully initiate an infection) does not qualitatively affect the results as  
we show on figure A.1 and A.2.

558

figure A.1 here
-----------------

For different values of  $n$  the trade-off curve has the saturating shape already  
560 described. The effect of an increase in  $n$  is to shift the curve to right. Note that  
even for the lowest possible value of  $n$  (which is two because we assume the  
562 dispersal stage is sexual) the curve is highly concave, which implies a stable  
evolutionary virulence.

564

figure A.2 here
-----------------

Figure A.2A and B show that the two optimal conversion strategies are also  
566 observed for any value of  $n$ .

568 **B Parasite's  $R_0$  with no deleterious effect of sexual parasites**

It is possible to assume that sexual parasites have no negative effect at all, as  
570 in (McKenzie and Bossert, 1997). Thus,  $u_2 = 0$ . figure 4 is then different.

figure B.1 here

572 On figure B.1, whatever the parasite growth rate ( $\varphi$ ), there is only a unique  
value of  $m$  maximising the  $R_0$ . In other words, if sexual parasites do not cause  
574 any harm to the main host, parasites should evolve towards high conversion  
rates.

576 **C Case with a linear transmission rate**

It is possible to assume that transmission is linearly correlated with the density  
578 of sexual parasites, *i.e.* that

$$\beta_{h \rightarrow v}(\varphi, m) = a \tilde{x}_2(\varphi, m) \tag{C.1}$$

where  $a$  is a constant describing the parasite transmission efficiency and  $\tilde{x}_2(\varphi, m)$   
580 is the density of sexual parasites for a given parasite growth rate  $\varphi$  and conversion rate  $m$ .

582 With this hypothesis, we obtain a less convex and more variable trade-off, as in our previous approach (Alizon and Van Baalen, 2005). Still, it is possible to  
584 study the influence of gamecytogenesis (*i.e.* parameter  $m$ ) on the parasite  $R_0$ .  
More precisely, what we are interested in is the consequences of deleterious  
586 effects of sexual parasites ( $u_2$ ) on the optimal conversion rate.

figure C.1 here

588 Figure C.1B reveals that if this deleterious effect is neglected (*i.e.*  $u_2 = 0$ ), then there is a clear optimal strategy for the parasite which should maximise  
590 its transmission rate. In contrast, the optimal conversion rate is much more variable if  $u_2 > 0$ . This result is similar to the result found with a sigmoid  
592 transmission function. It suggest that deleterious effect of sexual parasites is important and should be taken into account.

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Table 1

List of the notations used. Variables are indicated with a  $v$  and constants are indicated by their default values.

Notation	Default value	Description
$\varphi$	$v$	parasite within-host growth rate
$m$	$v$	parasite conversion rate
$x_1$	$v$	density of asexual parasites
$x_2$	$v$	density of sexual parasites
$y$	$v$	lymphocyte density
$\sigma_1$	1	killing rate of asexual parasites by the lymphocytes
$\sigma_2$	0.1	killing rate of sexual parasites by the lymphocytes
$b$	0.01	lymphocyte base-line production rate
$c_1$	0.1	proliferation rate of lymphocytes activated by asexuals
$c_2$	0.01	proliferation rate of lymphocytes activated by sexuals
$\delta$	1	lymphocyte mortality rate
$R_0$	$v$	parasite basic reproduction ratio
$\alpha$	$v$	virulence, <i>i.e.</i> infected host mortality du to the infection
$\beta$	$v$	transmission rate of the parasite
$\gamma$	$v$	host recovery
$S$	$v$	density of susceptible hosts
$a$	10	transmission constant
$M$	$v$	number of sexual parasites in a mosquito blood-meal
$\mu$	0.1	host natural death rate
$u_1$	0.05	deleterious effect of a asexual (replicating) parasites
$u_2$	0.05	deleterious effect of a sexual (non-replicating) parasites
$w$	0.01	lymphocyte detrimental effect

## Figure Captions

742 Fig. 1: Transmission rate of the parasite from its main host to the mosquito.  
The transmission function has a S-shape: at low sexual parasite densities the  
744 transmission is complicated and at high densities it saturates. Parameter val-  
ues are  $n = 40$ ,  $c_1 = 0.1$ ,  $c_2 = 0.01$ ,  $\sigma_1 = 1$ ,  $\sigma_2 = 0.1$ ,  $b = 0.01$ ,  $\delta = 1$ ,  
746  $a = 10$ .

Fig .2: Trade-off curve (A) and basic reproduction ratio curve (B). Dashed  
748 lines show the same functions assuming a linear transmission rate. On figure  
A, the black dot indicates the ESV of the plain curve and the grey dot indicates  
750 the ESV of the dashed curve. Parameter values are identical to figure 1 and  
 $\mu = 0.1$ ,  $u_1 = 0.05$ ,  $u_2 = 0.05$  and  $w = 0.01$ .

752 Fig. 3: Effect of host natural mortality ( $\mu$ ) on the trade-off curves (A) for  
a linear transmission function and (B) for a sigmoid transmission function.  
754 ESV are indicated by a large dot. Dashed lines are the tangent to the curves  
for various values of  $\mu$ . Parameter values are identical to figure 2. In green  
756  $\mu = 0.1$ , in red  $\mu = 0.05$ , in black  $\mu = 0.02$  and in blue  $\mu = 0.01$ .

Fig. 4: Effect of the parasite conversion rate ( $m$ ) and of the within-host growth  
758 rate ( $\varphi$ ) on the  $R_0$  value. Areas where the parasite's  $R_0$  is greater than unity  
are coloured in black. Note that if  $m \approx 1$  or if  $\varphi$  is small compared to  $m$ ,  
760 our results are not valid anymore (*cf.* the black crescent area). The darker the  
area, the higher  $R_0$ . Parameter values are that of figure 2.

762 Fig. 5: Effect of a treatment targeting either the asexual (A) or the sexual life-  
stage (B). Grey colours indicate the value of the  $R_0$  (the darker the area, the  
764 greater the  $R_0$ ) depending on the intensity of the treatment and on the parasite  
growth rate ( $\varphi$ ). The black and white dashed lines indicate the optimal value  
766 of  $\varphi$  for a given treatment intensity. In the white areas, the parasite cannot  
survive in the host population (*i.e.*  $R_0 < 1$ ). Parameter values are identical to  
768 figure 2.

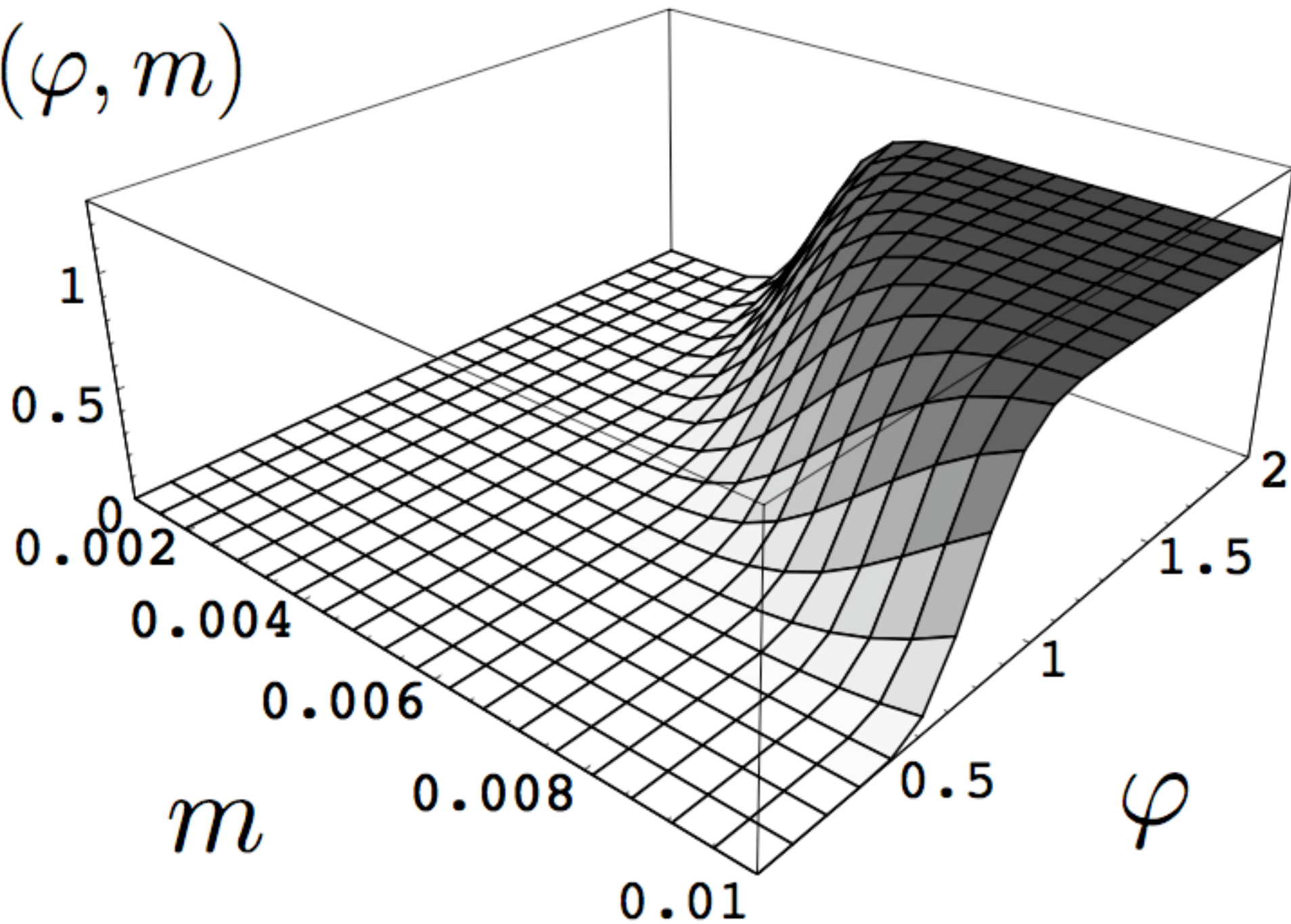
Fig. A.1: Trade-off curves for different values of  $n$ . On the dashed curve  $n = 2$ ,  
770 on the drawn curve  $n = 40$  and on the dotted curve  $n = 100$ . For further  
details, see figure 2.

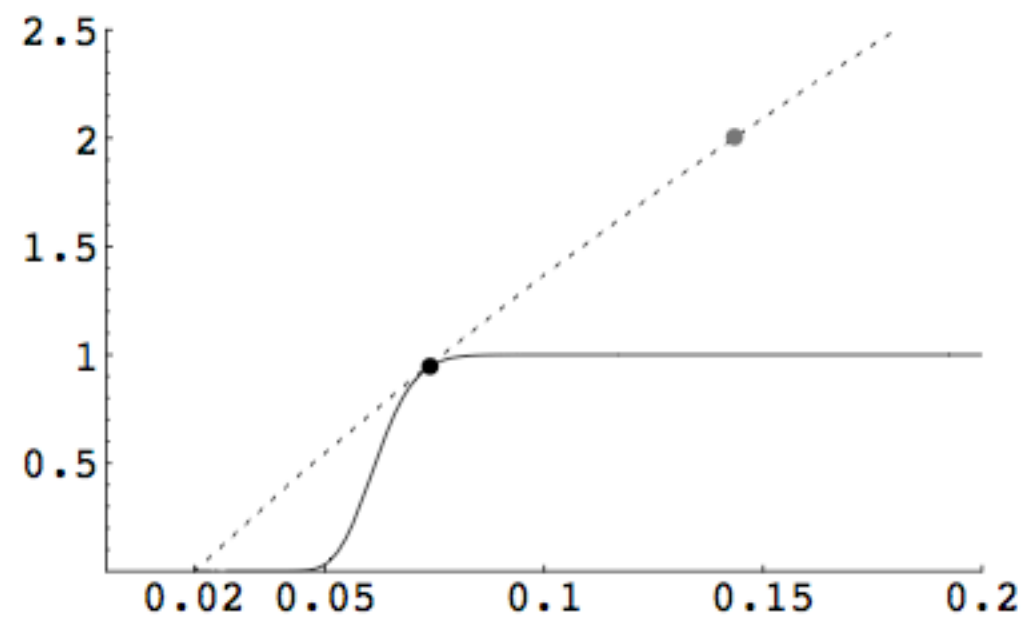
772 Fig. A.2: Effect of the parasite conversion rate ( $m$ ) and of the within-host  
growth rate ( $\varphi$ ) on the  $R_0$  value for  $n = 2$  (A) and  $n = 100$  (B). For further  
774 details, see figure 4.

Fig. B.1:  $R_0$  value depending on the parasite conversion rate ( $m$ ) and within-  
776 host growth rate ( $\varphi$ ) without gametocyte deleterious effect. Areas where the  
 $R_0$  is greater than unity are coloured in grey. The darker the area is, the higher  
778 the  $R_0$  is. Parameter values are identical to figure 4.

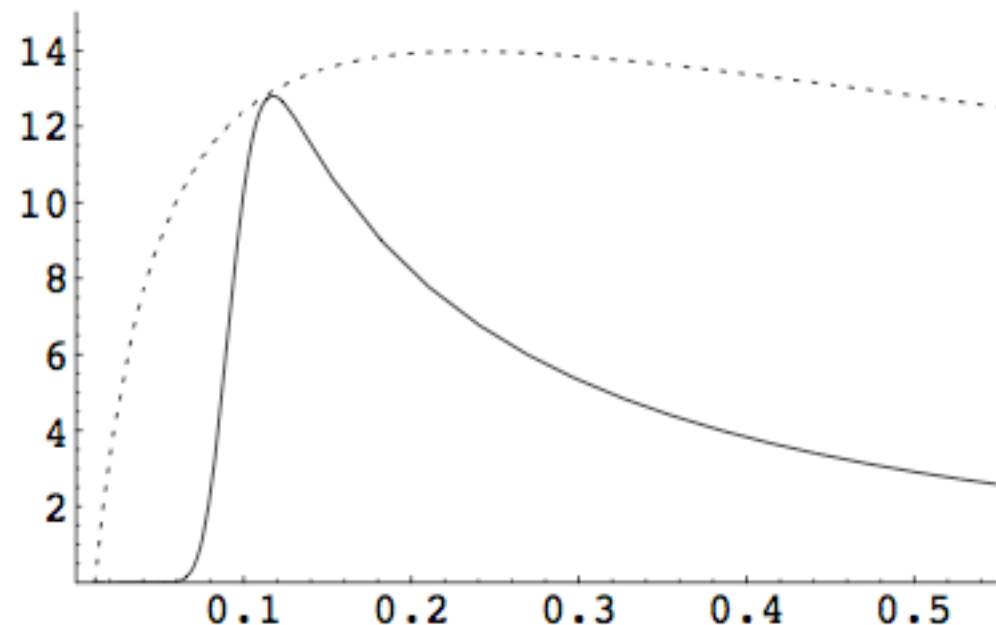
Fig. C.1:  $R_0$  of the parasite with (A) or without (B) gametocyte deleterious  
780 effects and with a linear transmission function. Here,  $\varphi = 1$  and other param-  
eter values are identical to figure 2 except parameter  $a$  in figure B which has  
782 been rescaled ( $a = 0.02$ ) to have similar maximum transmission value.

$$\beta_{h \rightarrow m}(\varphi, m)$$



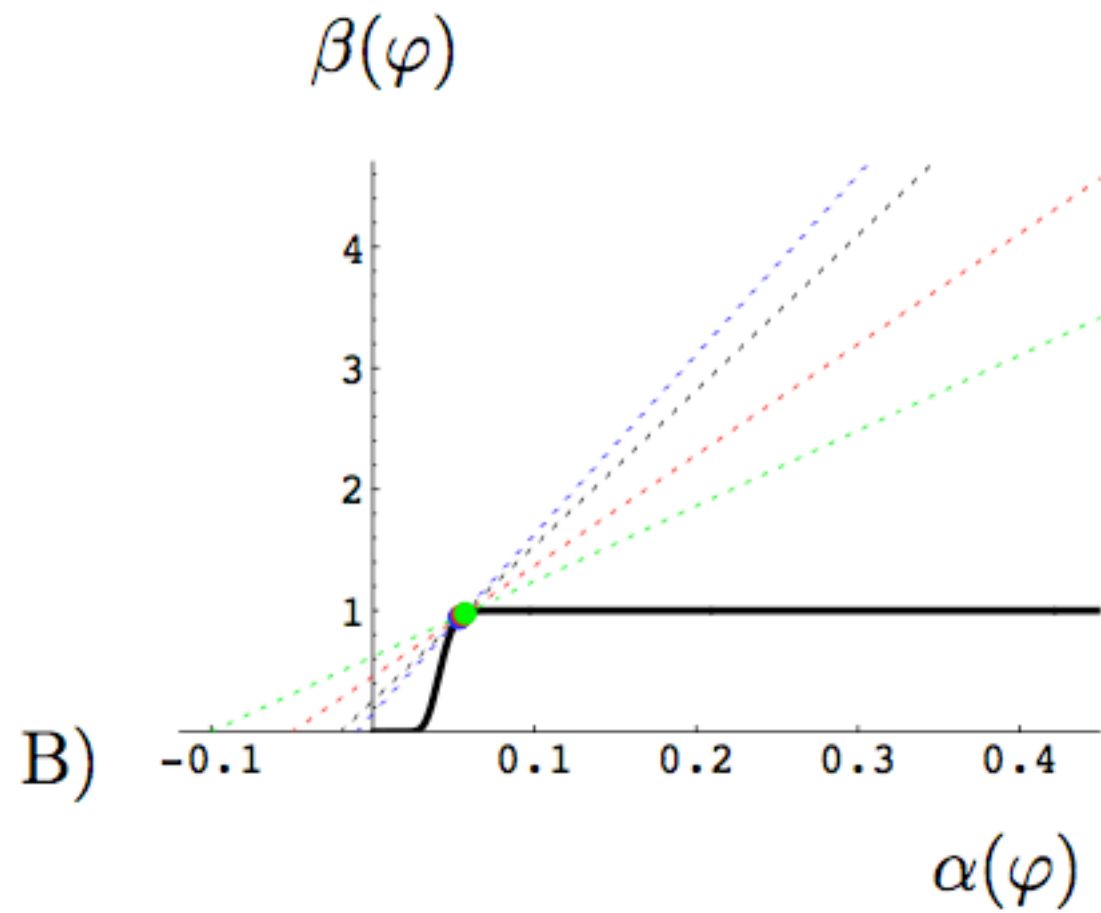
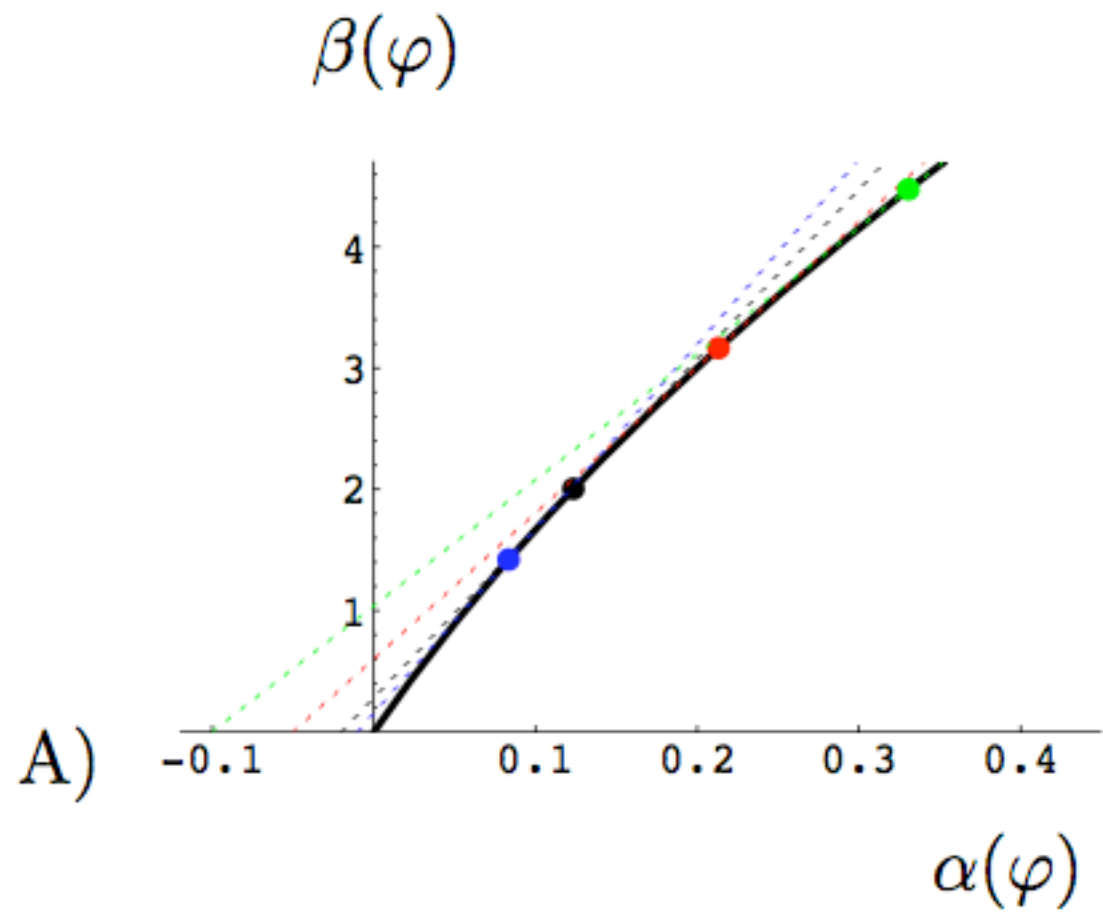
$\beta(\varphi)$ 

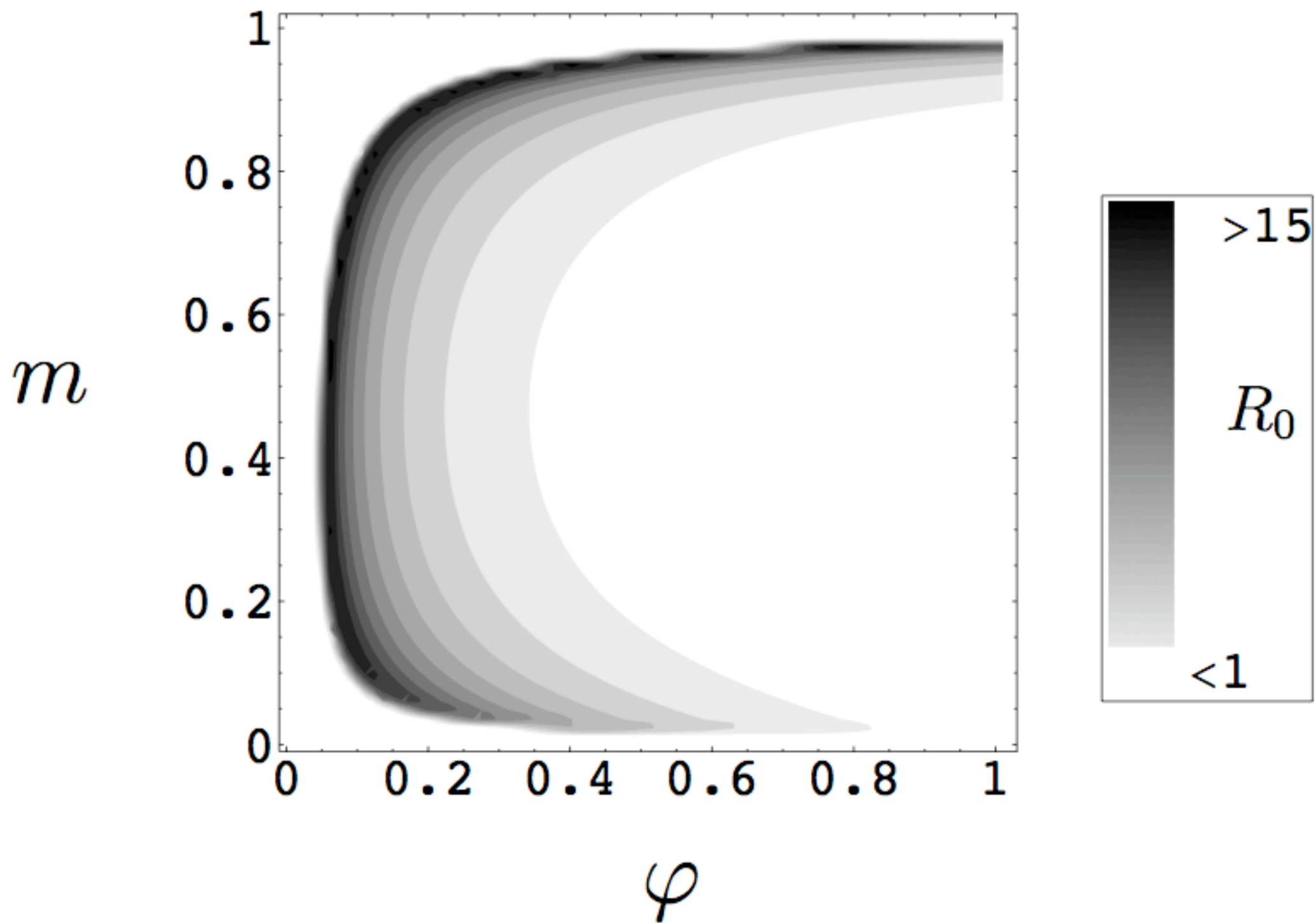
A)

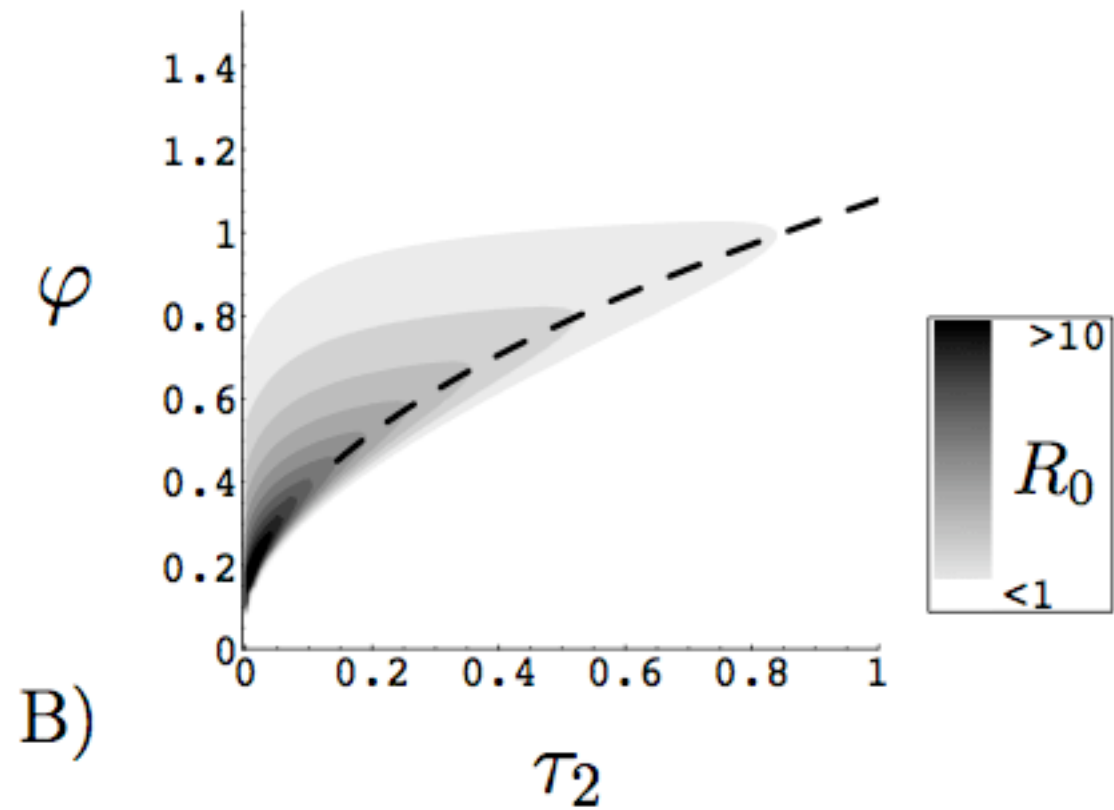
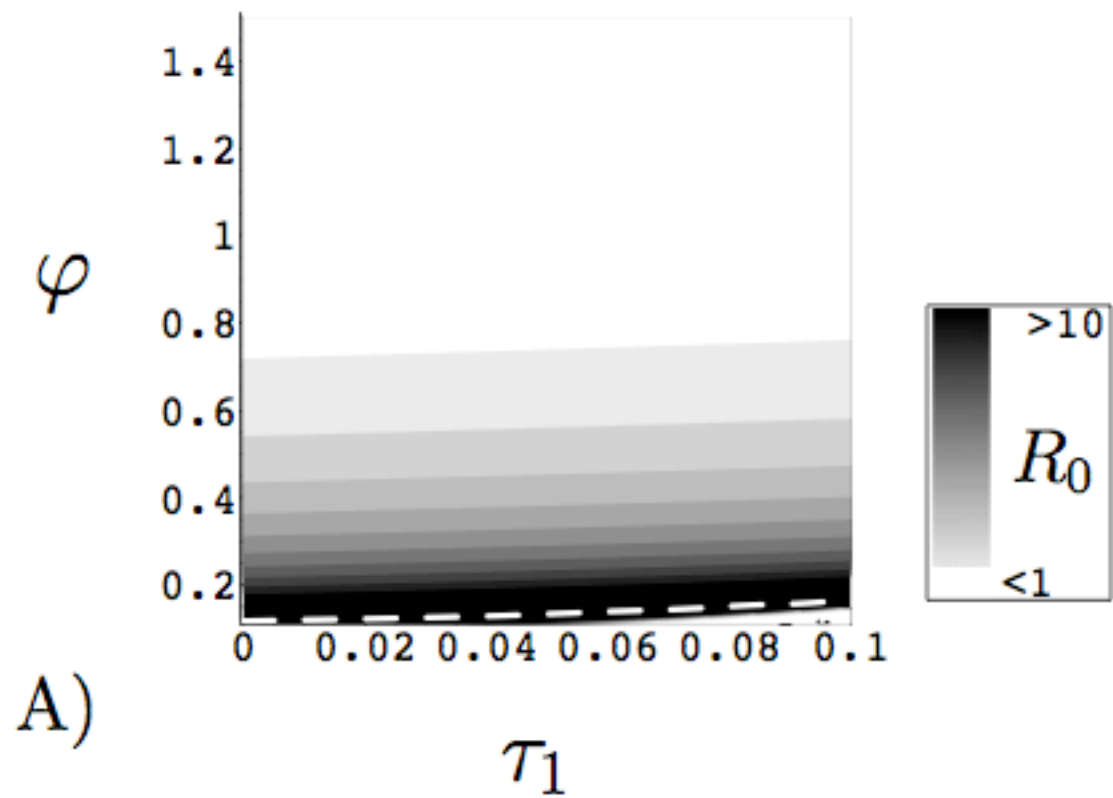
 $\mu + \alpha(\varphi)$  $R_0(\varphi)$ 

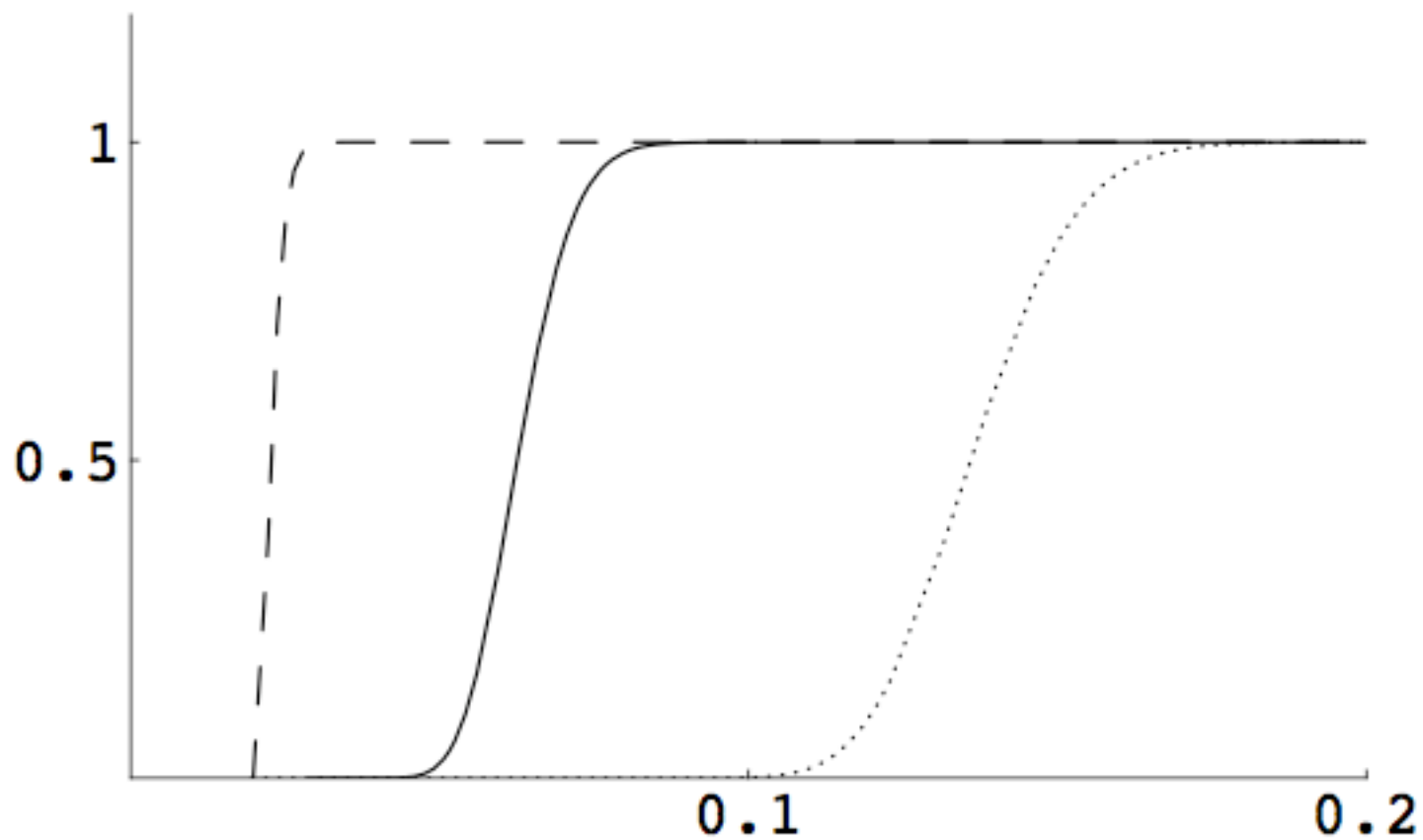
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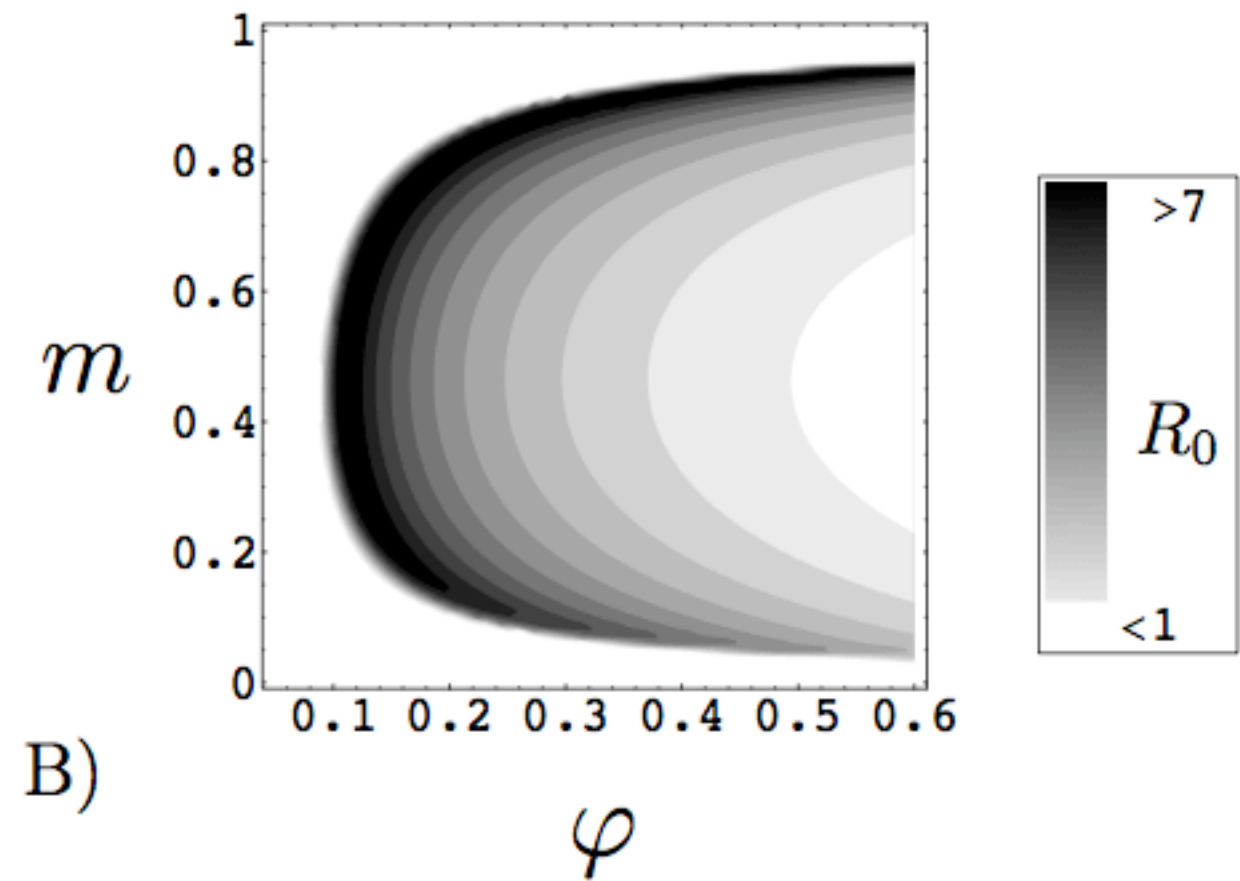
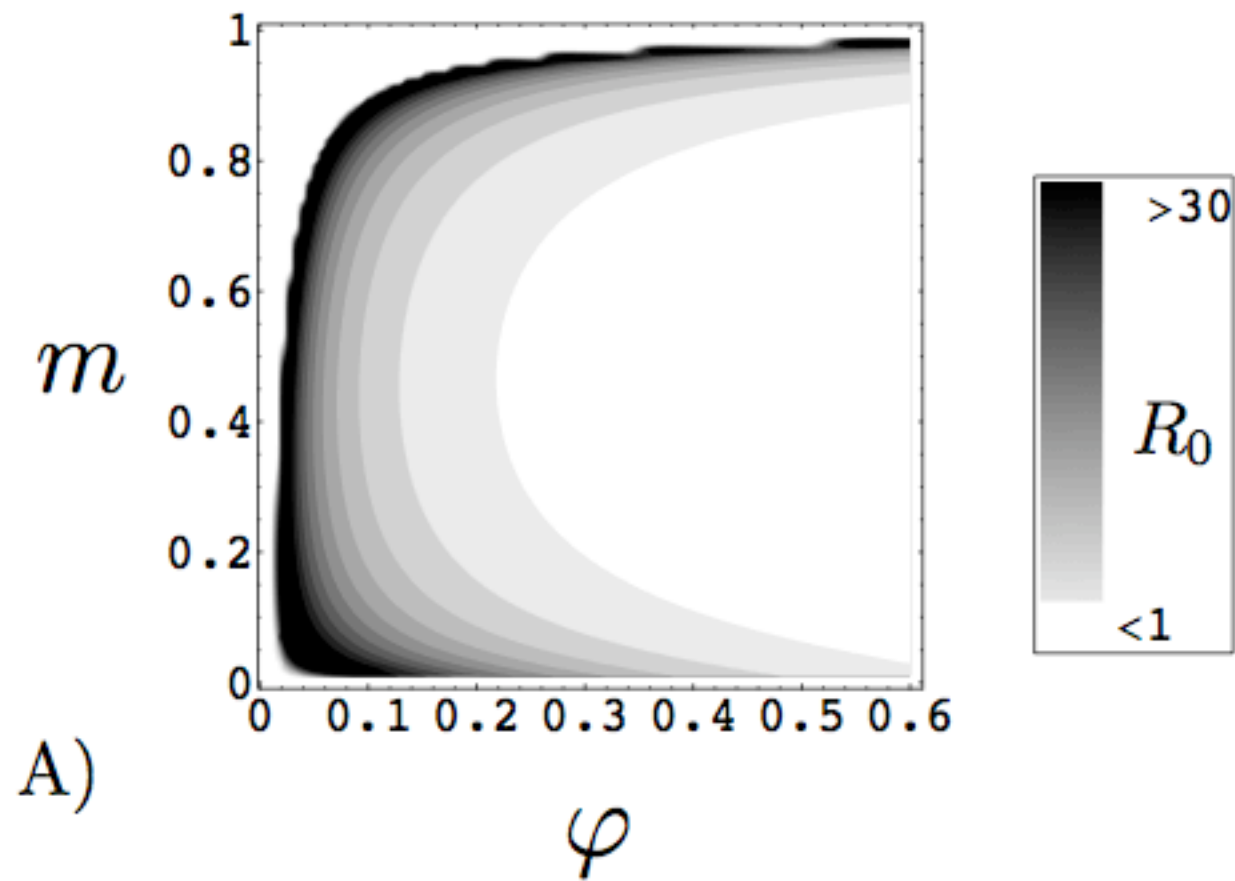
 $\varphi$

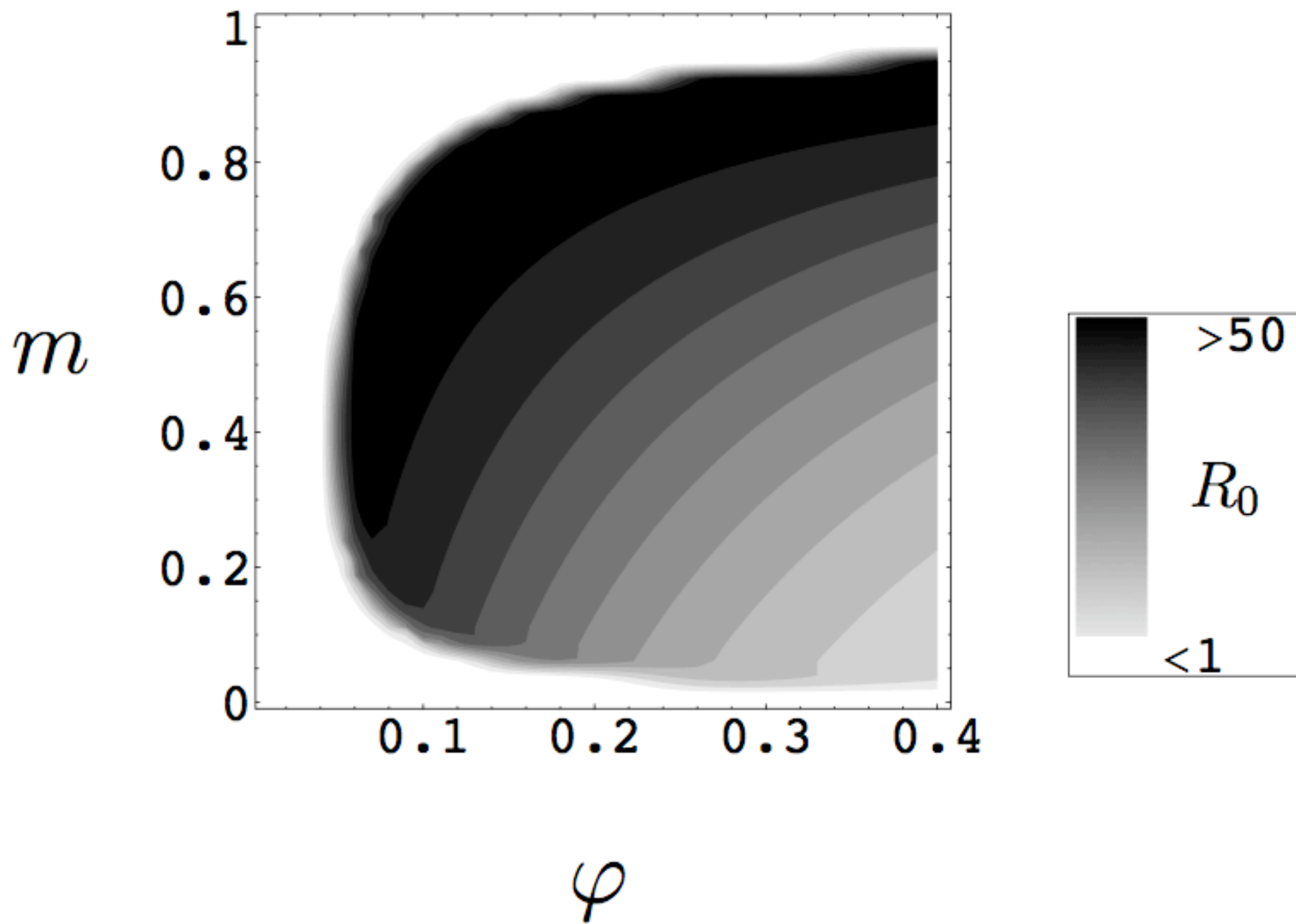




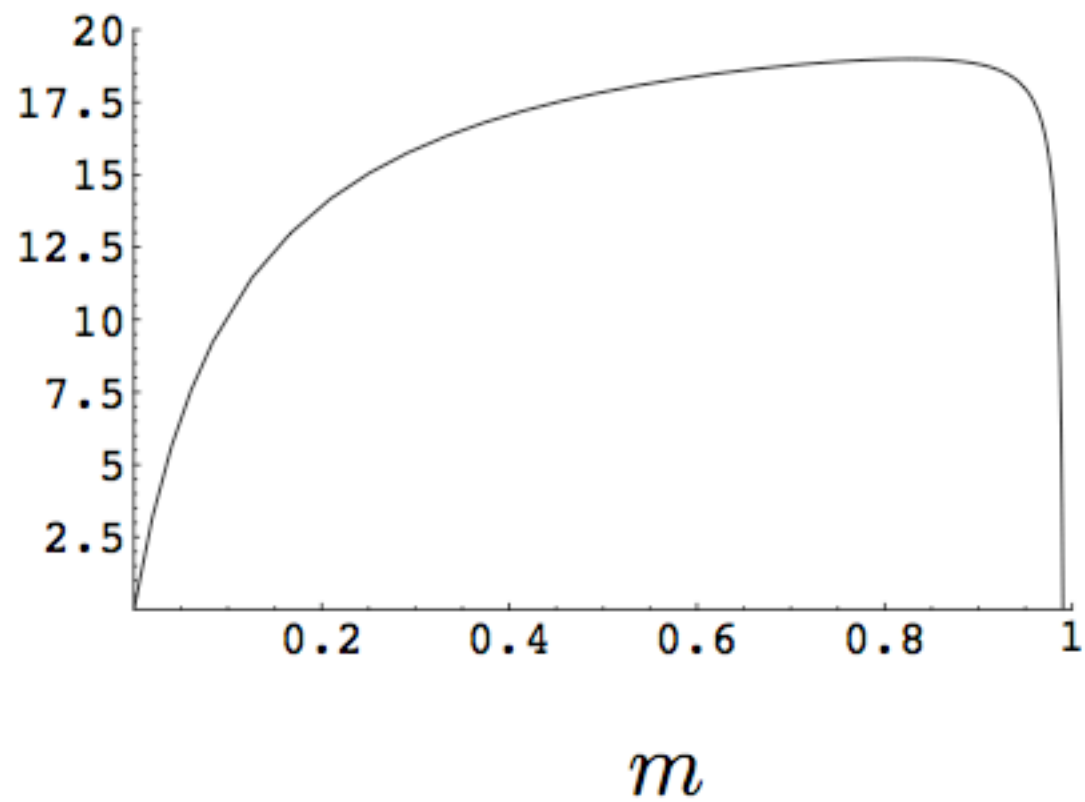


$\beta(\varphi)$  $\mu + \alpha(\varphi)$





$R_0(1, m)$



$R_0(1, m)$

