

Transmission-virulence trade-offs in vector-borne diseases

Samuel Alizon, Minus van Baalen

► **To cite this version:**

Samuel Alizon, Minus van Baalen. Transmission-virulence trade-offs in vector-borne diseases. Theoretical Population Biology, Elsevier, 2008, 74, pp.6 - 15. 10.1016/j.tpb.2008.04.003 . hal-01396035

HAL Id: hal-01396035

<https://hal.archives-ouvertes.fr/hal-01396035>

Submitted on 13 Nov 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Transmission-virulence trade-offs in vector-borne diseases

Samuel Alizon^{a,b,c} Minus van Baalen^a

^a*Laboratoire Fonctionnement et évolution des systèmes écologiques, Université
Paris 6, ENS, CNRS – UMR 7625, case 237, 7 quai Saint-Bernard F-75252 Paris
cedex 05, France, Tel: +33.1.44.27.58.61, Fax: +33.1.44.27.35.16*

^b*Department of Mathematics & Statistics and Department of Biology, Queen's
University, Kingston (ON), K7L3N6, Canada*

^c*Corresponding author.*

Email addresses: samuel@mast.queensu.ca, minus.van.baalen@ens.fr

Approx. 5900 words in the main text (excluding figure captions), 138 words in the
abstract, 57 references and 3 on-line appendixes.

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

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

$$\frac{dx_1}{dt} = (\varphi(1 - m) - \sigma_1 y) x_1 \tag{1}$$

$$\frac{dx_2}{dt} = \varphi m x_1 - \sigma_2 y x_2$$

where φ is the parasite intrinsic per capita growth rate, σ_1 the killing rate of
 108 asexual parasites by the immune system, σ_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 δ 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 β , the
170 recovery rate γ , the natural host mortality μ , the disease-induced mortality
(or virulence) α 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 μL 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 μL 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 μL (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 φ
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 φ 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 φ 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 φ (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 φ 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
 φ^* 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 (μ)
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 σ_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 ϕ (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 φ 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 (τ_1) to x_1 . In the second case, the treat-
326 ment targets sexual life-stages and we add an extra mortality term (τ_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 τ_1 and τ_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 τ_1) is not very efficient at reducing the R_0 . In
contrast, targeting the sexual parasite (*i.e.* increasing τ_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 φ 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 (μ) 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.

4.5 Acknowledgements

We thank L. Lambrechts and J. Koella for helpful discussions about malaria. We also thank S. Fellous, S. Lion, N. Mideo, A. L. Graham, V. Ganusov and two anonymous reviewers for helpful comments on previous versions of this article.

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 (φ), 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 φ 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
study the influence of gamecytogenesis (*i.e.* parameter m) on the parasite R_0 .
584 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
its transmission rate. In contrast, the optimal conversion rate is much more
590 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.

594 **References**

Alizon, S., van Baalen, M., submitted Acute or chronic? models combining
596 immune system dynamics and parasite evolution explain the outcome of
infections (synthesis).

598 Alizon, S., Van Baalen, M., 2005. Emergence of a convex trade-off between
transmission and virulence. *Am. Nat.* 165 (6), E155–E167.

600 Anderson, R. M., 1994. Mathematical studies of parasitic infections and im-
munity. *Science* 264, 1884–1886.

602 Anderson, R. M., May, R. M., 1991. *Infectious Diseases of Humans. Dynamics
and Control.* Oxford University Press, Oxford.

604 André, J.-B., Gandon, S., 2006. Vaccination, within-host dynamics, and viru-
lence evolution. *Evolution* 60 (1), 13–23.

606 Anker, M., Schaaf, D., 2002. Who report on global surveillance of epidemic-
prone infectious diseases. Tech. Rep. WHO/CDS/CSR/ISR/2000.1, World
608 Health Organisation, Genève.

Boyd, M. F., 1949. A comprehensive survey of all aspects of this group of
610 diseases from a global standpoint, *malariology* Edition. W. B. Saunders,
Philadelphia, Ch. Epidemiology: factors related to the definitive host, pp.
612 608–697.

Brown, S. P., Hochberg, M. E., Grenfell, B. T., 2002. Does multiple infection
614 select for raised virulence? *Trends Microbiol.* 10, 401–405.

Buckling, A., Read, A. F., 2001. The effect of partial host immunity on the
616 transmission of malaria parasites. *Proc. R. Soc. Lond. B* 268 (1483), 2325–
2330.

618 Carter, R., Mendis, K. N., 2002. Evolutionary and historical aspects of the
burden of malaria. *Clin. Microbiol. Rev.* 15 (4), 564–594.

- 620 Davies, C. M., Webster, J. P., Woolhous, M. E., 2001. Trade-offs in the evolu-
tion of virulence in an indirectly transmitted macroparasite. Proc. R. Soc.
622 Lond. B 268 (1464), 251–257.
- Day, K. P., Koella, J. C., Nee, S., Gupta, S., Read, A. F., 1992. Population
624 genetics and dynamics of *Plasmodium falciparum*: an ecological view. Par-
asitology 104, S35–S52.
- 626 Day, T., 2001. Parasite transmission modes and the evolution of virulence.
Evolution 55 (12), 2389–2400.
- 628 Day, T., 2002. The evolution of virulence in vector-borne and directly trans-
mitted parasites. Theor. Popul. Biol. 62, 199–213.
- 630 de Roode, J. C., Helinski, M. E. H., Anwar, M. A., Read, A. F., 2005. Dynam-
ics of multiple infection and within-host competition in genetically diverse
632 malaria infections. Am. Nat. 166 (5), 531–542.
- Dimopoulos, G., 2003. Insect immunity and its implication in mosquito-
634 malaria interactions. Cell Microbiol. 5 (1), 3–14.
- Drakeley, C. J., Secka, I., Correa, S., Greenwood, B. M., Targett, G. A., 1999.
636 Host haematological factors influencing the transmission of plasmodium fal-
ciparum gametocytes to *Anopheles gambiae* s.s. mosquitoes. Trop. Med. Int.
638 Health. 4 (2), 131–138.
- Dyer, M., Day, K. P., 2000. Commitment to gametocytogenesis in *Plasmodium*
640 *falciparum*. Parasitol. Today 16 (3), 102–107.
- Ebert, D., Bull, J. J., 2003. Challenging the trade-off model for the evolution
642 of virulence: is virulence management feasible? Trends Microbiol. 11 (1),
15–20.
- 644 Eichner, M., Diebneti, H. H., Molineaux, L., Collins, W. E., Jeffery, G. M., Di-
etz, K., 2001. Genesis, sequestration and survival of *Plasmodium falciparum*
646 gametocytes: parameter estimates from fitting a model to malariatherapy

- data. *Trans. Roy. Soc. Trop. Med. Hyg.* 95, 497–501.
- 648 Ewald, P. W., 1983. Host-parasite relations, vectors, and the evolution of disease severity. *Annu. Rev. Ecol. Evol. Syst.* 14, 465–485.
- 650 Ewald, P. W., 1994. *Evolution of Infectious Disease*. Oxford University Press, Oxford.
- 652 Ferguson, H. M., Mackinnon, M. J., Chan, B. H., Read, A. F., 2003. Mosquito mortality and the evolution of malaria virulence. *Evolution* 57 (12), 2792–
654 2804.
- Gandon, S., 1998. The curse of the pharaoh. *Proc. R. Soc. Lond. B* 265, 1545–
656 1552.
- Gandon, S., 2004. Evolution of multihost parasites. *Evolution* 58 (3), 455–469.
- 658 Gandon, S., Mackinnon, M. J., Nee, S., Read, A. F., 2001. Imperfect vaccines and the evolution of pathogen virulence. *Nature* 414, 751–756.
- 660 Ganusov, V. V., Antia, R., 2003. Trade-offs and the evolution of virulence of microparasites: do details matter? *Theor. Popul. Biol.* 64, 211–220.
- 662 Gilchrist, M. A., Coombs, D., 2006. Evolution of virulence: Interdependence, constraints, and selection using nested models. *Theor. Popul. Biol.* 69 (2),
664 145–153.
- Graham, A. L., Allen, J. E., Read, A. F., 2005. Evolutionary causes and consequences of immunopathology. *Annu. Rev. Ecol. Evol. Syst.* 36, 373–397.
- 666 Heffernan, J. M., Smith, R. J., Wahl, L. M., 2005. Perspectives on the basic reproductive ratio. *J. R. Soc. Interface* 2, 281–293.
- 668 Jeffery, G. M., 1956. Blood meal volume in *Anopheles quadrimaculatus*, *A. albimanus*, and *Aedes aegypti*. *Exp. Parasitol.* 5, 371–375.
- 672 Kelley, C. F., Barbour, J. D., Hecht, F. M., 2007. The relation between symptoms, viral load, and viral load set point in primary hiv infection. *J. Acquir.*

- Immune Defic. Syndr. 45 (4), 445–448.
- 674 Koella, J. C., Antia, R., 1995. Optimal pattern of replication and transmission
for parasites with two stages in their life cycle. *Theor. Popul. Biol.* 47, 227–
676 291.
- Kwiatkowski, D., 1991. Cytokines and anti-disease immunity to malaria. *Res.*
678 *Immunol.* 142 (8), 707–712.
- Levin, B. R., Bull, J. J., 1994. Short-sighted evolution and the virulence of
680 pathogenic microorganisms. *Trends Microbiol.* 2 (3), 76–81.
- Lipsitch, M., Moxon, E. R., 1997. Virulence and transmissibility of pathogens:
682 what is the relationship? *Trends Microbiol.* 5, 31–37.
- Mackinnon, M. J., Read, A. F., 1999a. Genetic relationships between para-
684 site virulence and transmission in the rodent malaria *Plasmodium chabaudi*.
Evolution 53, 689–703.
- 686 Mackinnon, M. J., Read, A. F., 1999b. Selection for high and low virulence
in the malaria parasite *Plasmodium chabaudi*. *Proc. R. Soc. Lond. B* 266,
688 741–748.
- Mackinnon, M. J., Read, A. F., 2004a. Immunity promotes virulence evolution
690 in a malaria model. *PLoS. Biol.* 2 (9), 1286–1292.
- Mackinnon, M. J., Read, A. F., 2004b. Virulence in malaria: an evolutionary
692 viewpoint. *Philos. Trans. R. Soc. B* 359, 965–986.
- McKenzie, F. E., Bossert, W. H., 1997. The dynamics of *Plasmodium falciparum*
694 blood-stage infection. *J. Theor. Biol.* 188, 127–140.
- Mideo, N., Alizon, S., Day, T., Linking within- and between-host disease dy-
696 namics.
- Mideo, N., Day, T., 2008. The evolution of reproductive restraint in malaria.
698 *Proc. R. Soc. Lond. B* 275, 1217–1224.
- Molineaux, L., Dietz, K., 1999. Review of intra-host models of malaria. *Paras-*

700 sitologia 41, 221–231.

Paul, R. E. L., Bonnet, S., Boudin, C., Tchuinkam, T., Robert, V., 2007.
702 Aggregation in malaria parasites places limits on mosquito infection rates.
Infect. Genet. Evol. 7, 577–586.

704 Paul, R. E. L., Lafond, T., Müller-Graf, C. D. M., Nithiuthai, S., Brey, P. T.,
Koella, J. C., 2004. Experimental evaluation of the relationship between
706 lethal or non-lethal virulence and transmission success in malaria parasite
infections. BMC Evol. Biol. 4, 30.

708 Råberg, L., de Roode, J. C., Bell, A. S., Stamou, P., Gray, D., Read, A. F.,
2006. The role of immune-mediated apparent competition in genetically
710 diverse malaria infections. Am. Nat. 168 (1), in press.

Read, A. F., Taylor, L. H., 2001. The ecology of genetically diverse infections.
712 Science 292, 1099–1102.

Recker, M., Nee, S., Bull, P. C., Kinyanjui, S., Marsh, K., Newbold, C., Gupta,
714 S., 2004. Transient cross-reactive immune responses can orchestrate anti-
genetic variation in malaria. Nature 429 (6991), 555–558.

716 Regoes, R. R., Ebert, D., Bonhoeffer, S., 2002. Dose-dependent infection rates
of parasites produce the allee effect in epidemiology. Proc. R. Soc. Lond. B
718 269, 271–279.

Schall, J. J., 2000. Transmission success of the malaria parasite *Plasmodium*
720 *mexicanum* into its vector: role of gametocyte density and sex ratio. Para-
sitology 121 (06), 575–580.

722 Taylor, L. H., Read, A. F., 1997. Why so few transmission stages? reproductive
restraint by malaria parasites. Parasitol. Today 13 (4), 135–140.

724 Van Baalen, M., 1998. Coevolution of recovery ability and virulence. Proc. R.
Soc. Lond. B 265, 317–325.

726 Van Baalen, M., Sabelis, M. W., 1995a. The dynamics of multiple infection

- and the evolution of virulence. *Am. Nat.* 146, 881–910.
- 728 Van Baalen, M., Sabelis, M. W., 1995b. The scope for virulence management:
A comment on Ewald’s view on the evolution of virulence. *Trends Microbiol.*
730 3, 414–416.
- Van der Kolk, M., Tebo, A. E., Nimpaye, H., Ndombol, D. N., Sauerwein,
732 R. W., Eling, W. M., 2003. Transmission of *Plasmodium falciparum* in urban
yaounde, cameroon, is seasonal and age-dependent. *Trans. Roy. Soc. Trop.*
734 *Med. Hyg.* 97 (4), 375–379.
- World Health Organization, 2003. The africa malaria report. Tech. Rep.
736 WHO/CDS/MAL/2003.1093, WHO & UNICEF, Genève.
- Zimmerman, P. A., Mehlotra, R. K., Kasehagen, L. J., Kazura, J. W., 2004.
738 Why do we need to know more about mixed *Plasmodium* species infections
in humans? *Trends Parasitol.* 20 (9), 440–447.

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
φ	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
σ_1	1	killing rate of asexual parasites by the lymphocytes
σ_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
δ	1	lymphocyte mortality rate
R_0	v	parasite basic reproduction ratio
α	v	virulence, <i>i.e.</i> infected host mortality due to the infection
β	v	transmission rate of the parasite
γ	v	host recovery
S	v	density of susceptible hosts
a	10	transmission constant
M	v	number of sexual parasites in a mosquito blood-meal
μ	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 (μ) 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 μ . 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 (φ) 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 φ 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 (φ). The black and white dashed lines indicate the optimal value
766 of φ 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.

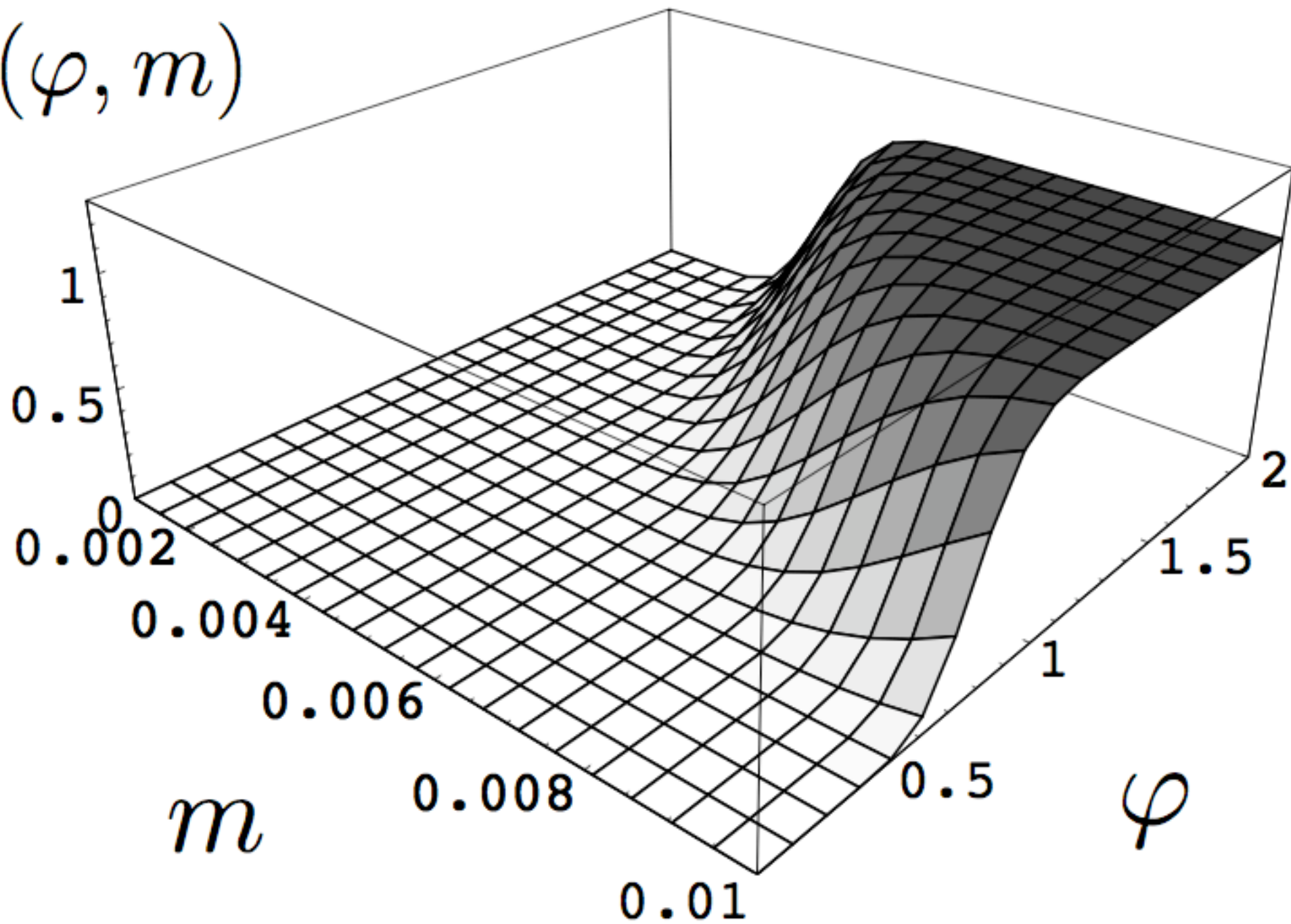
Fig. A.1: Trade-off curves for different values of n . On the dashed curve $n = 2$,
770 on the drawn curve $n = 40$ and on the dotted curve $n = 100$. For further
details, see figure 2.

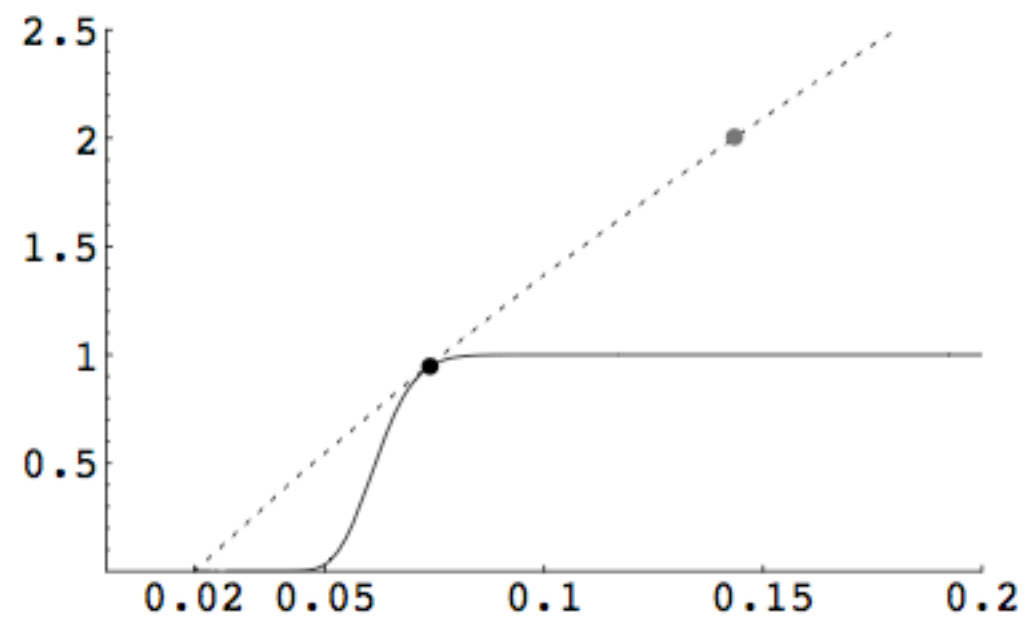
772 Fig. A.2: Effect of the parasite conversion rate (m) and of the within-host
growth rate (φ) on the R_0 value for $n = 2$ (A) and $n = 100$ (B). For further
774 details, see figure 4.

Fig. B.1: R_0 value depending on the parasite conversion rate (m) and within-
776 host growth rate (φ) 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.

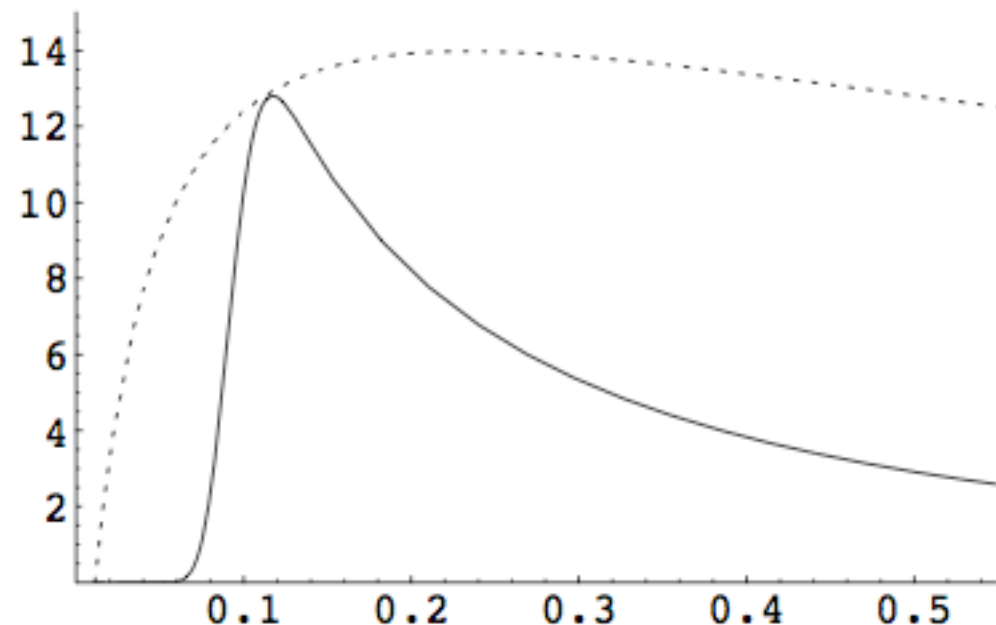
Fig. C.1: R_0 of the parasite with (A) or without (B) gametocyte deleterious
780 effects and with a linear transmission function. Here, $\varphi = 1$ and other param-
eter values are identical to figure 2 except parameter a in figure B which has
782 been rescaled ($a = 0.02$) to have similar maximum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

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



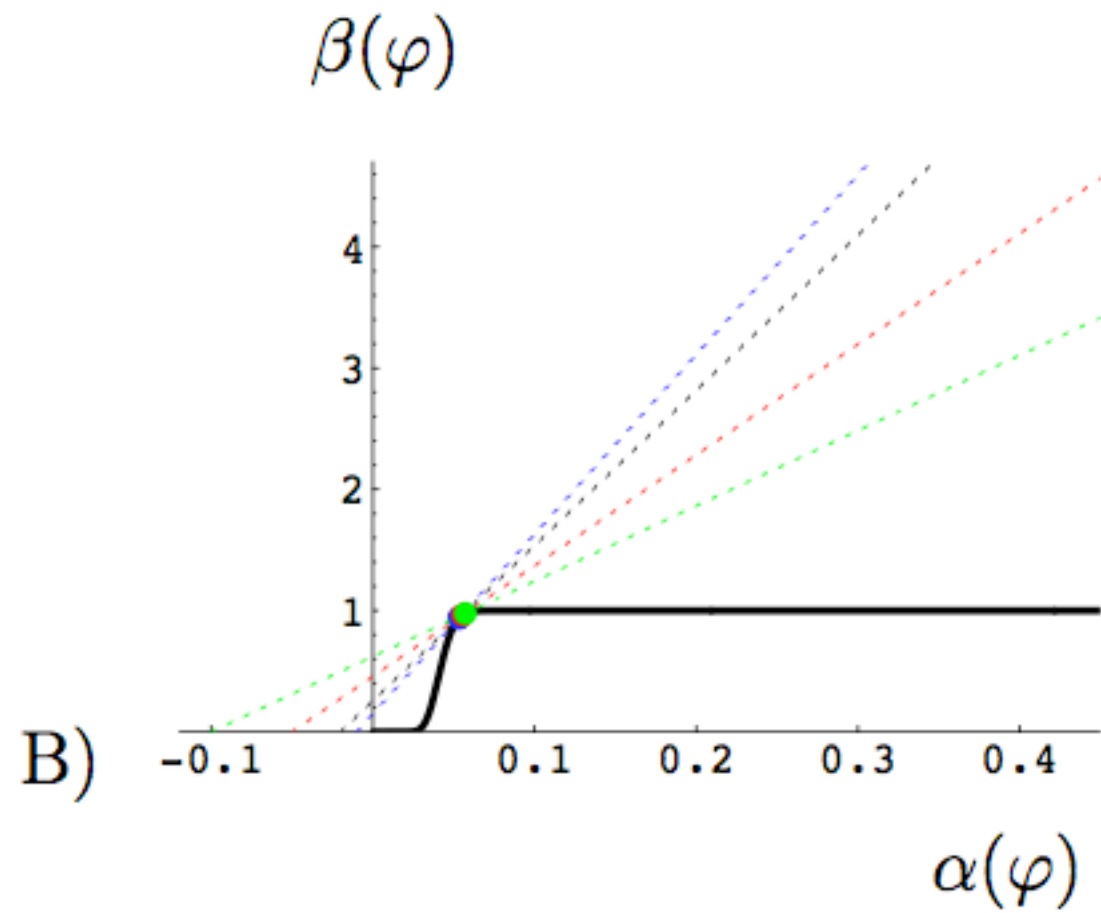
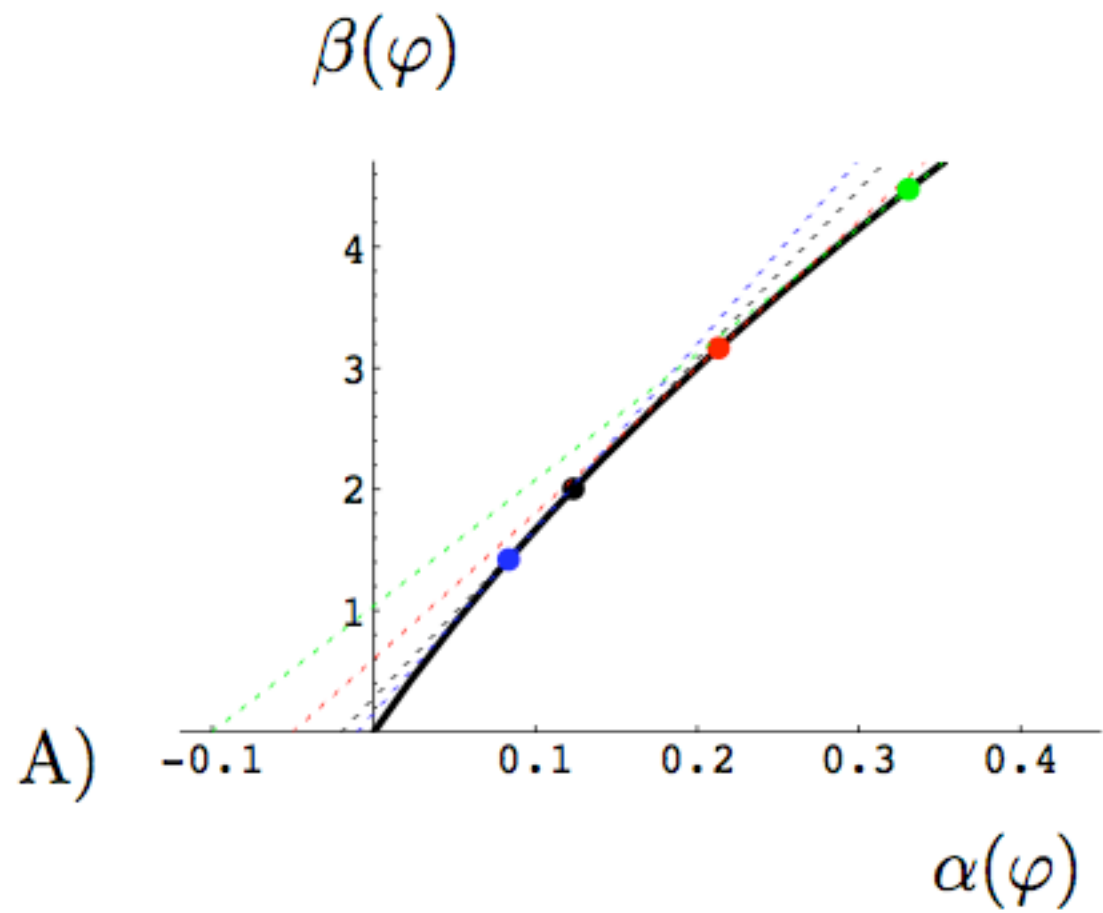
$\beta(\varphi)$ 

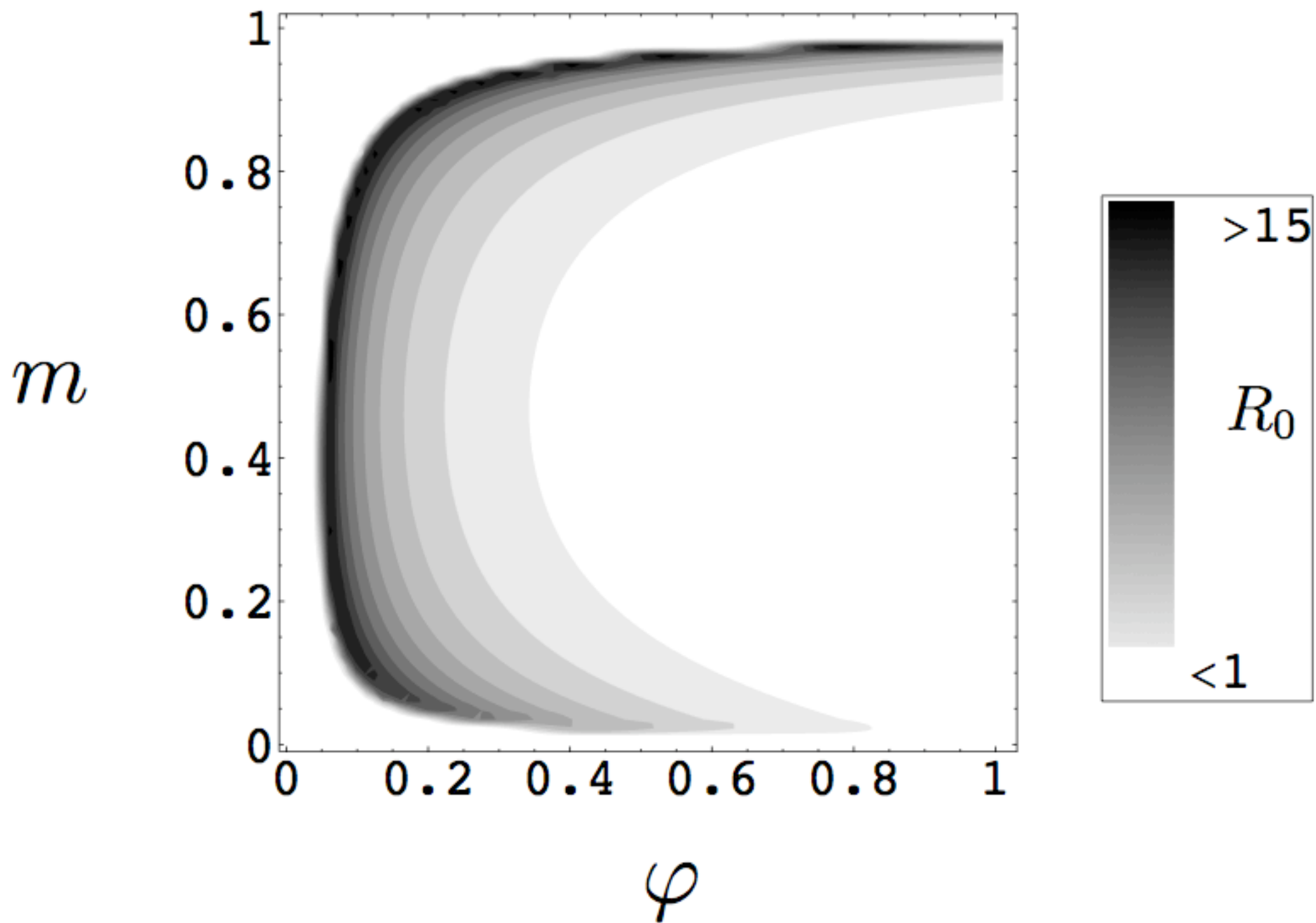
A)

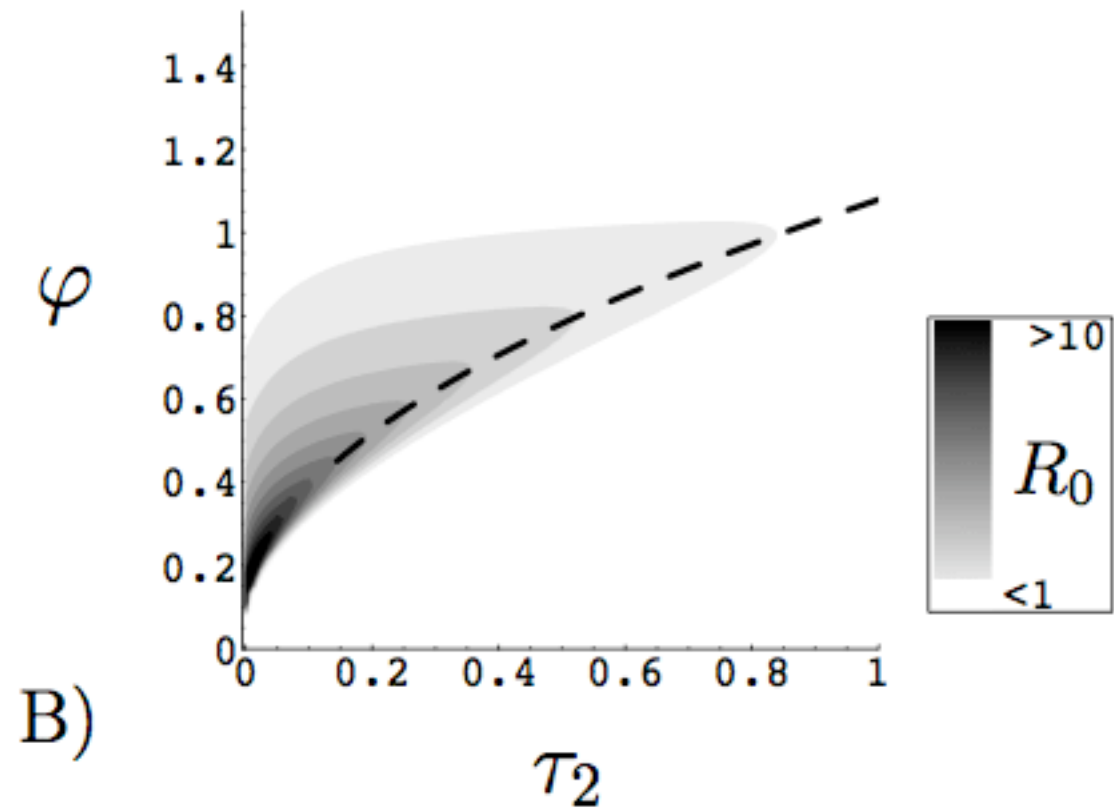
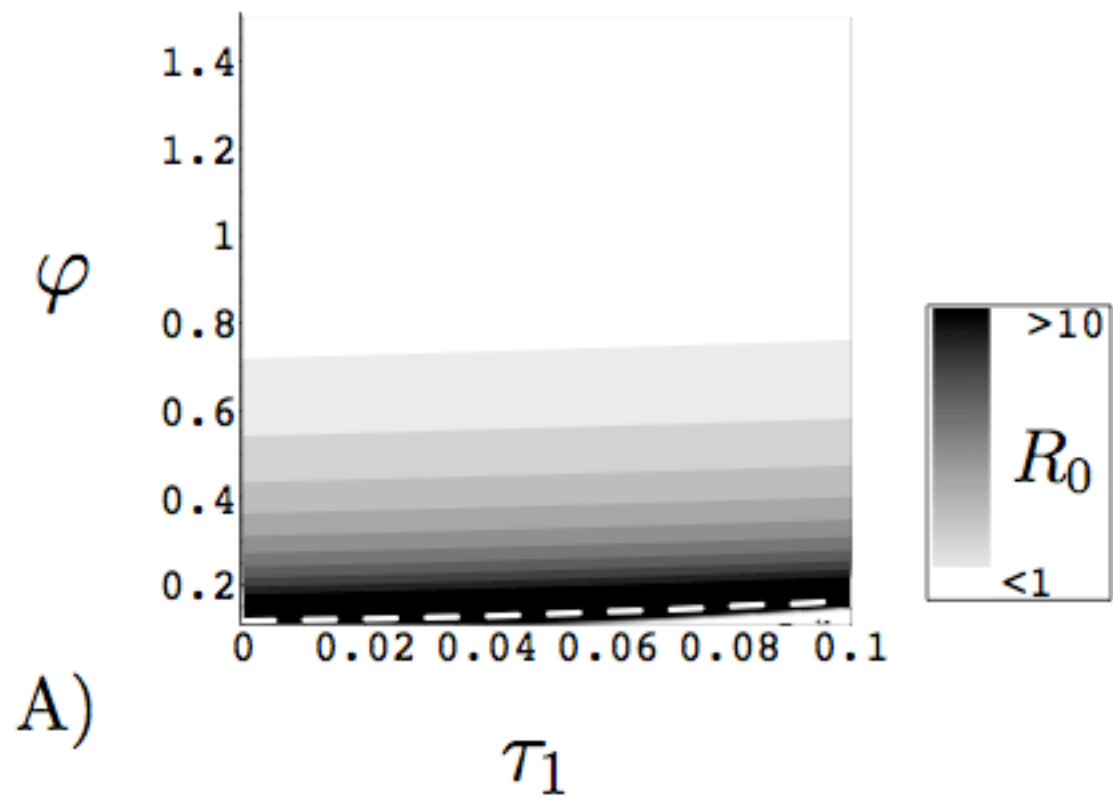
 $\mu + \alpha(\varphi)$ $R_0(\varphi)$ 

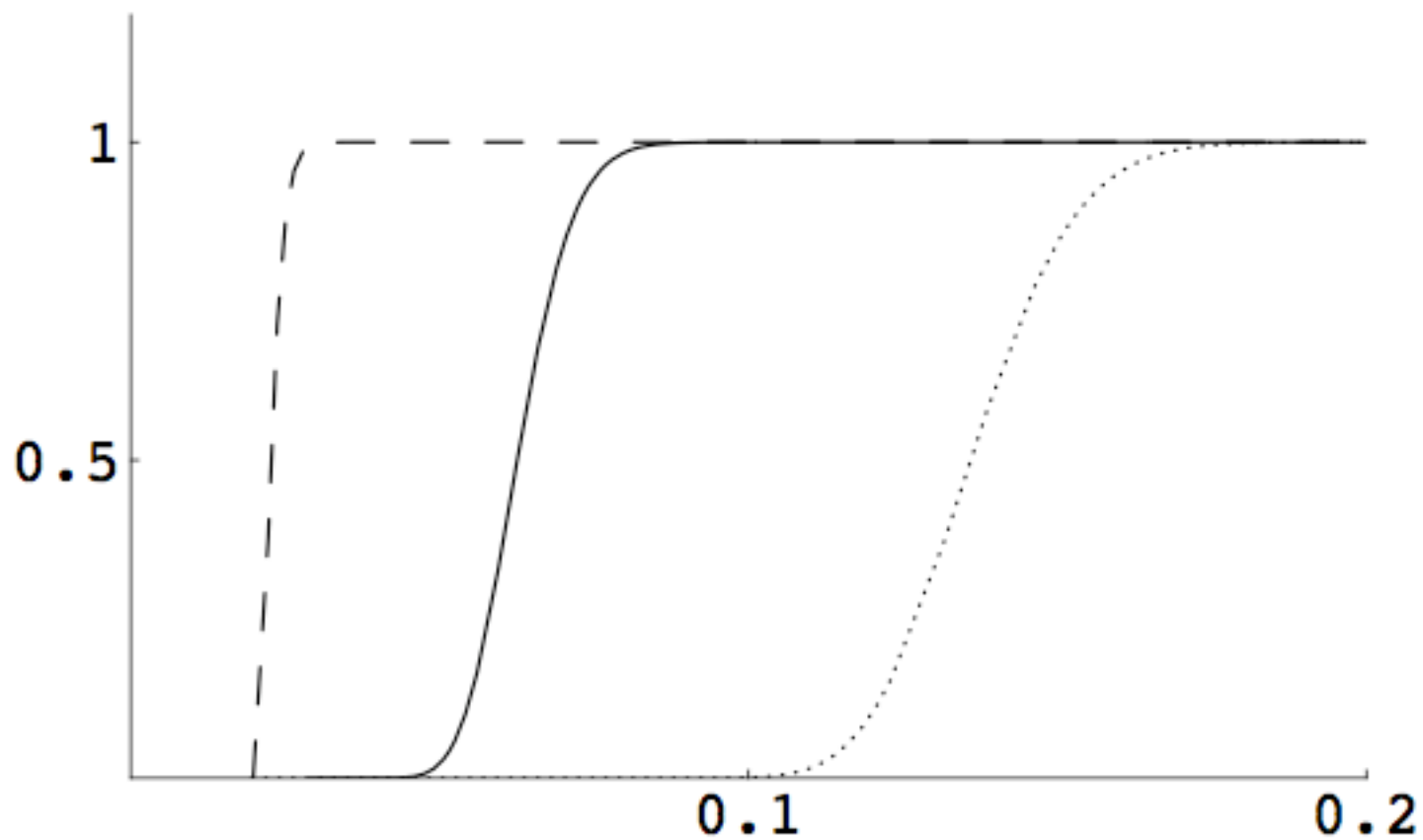
B)

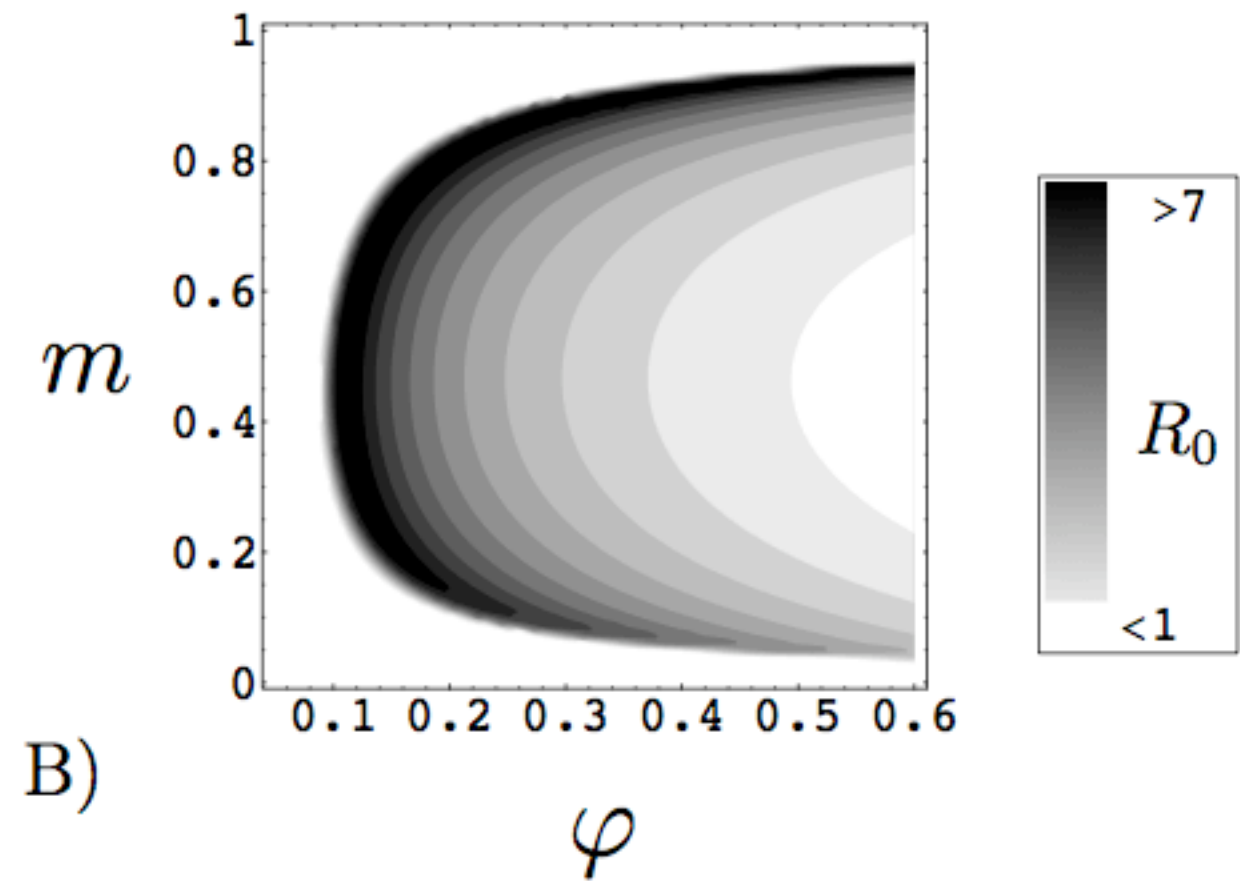
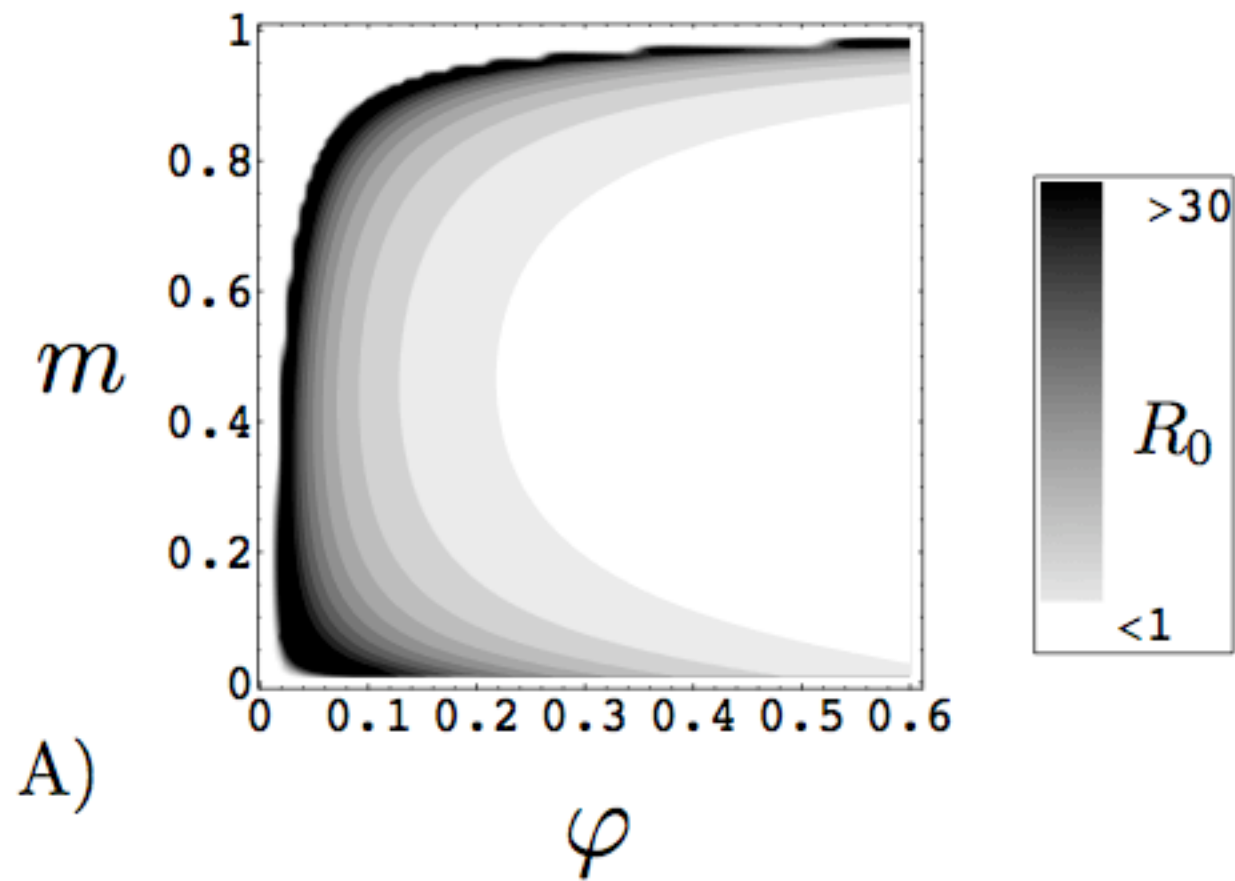
 φ

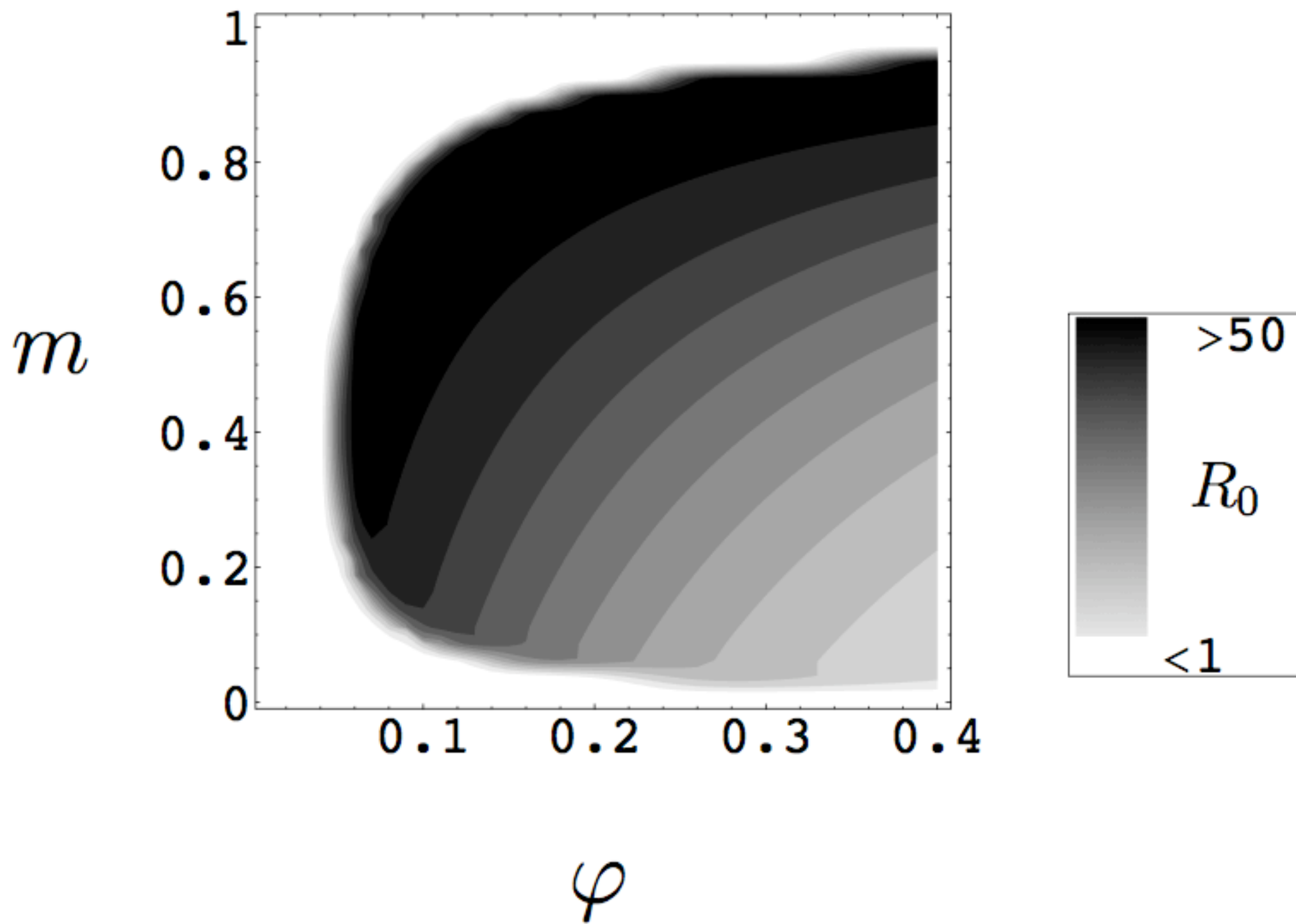




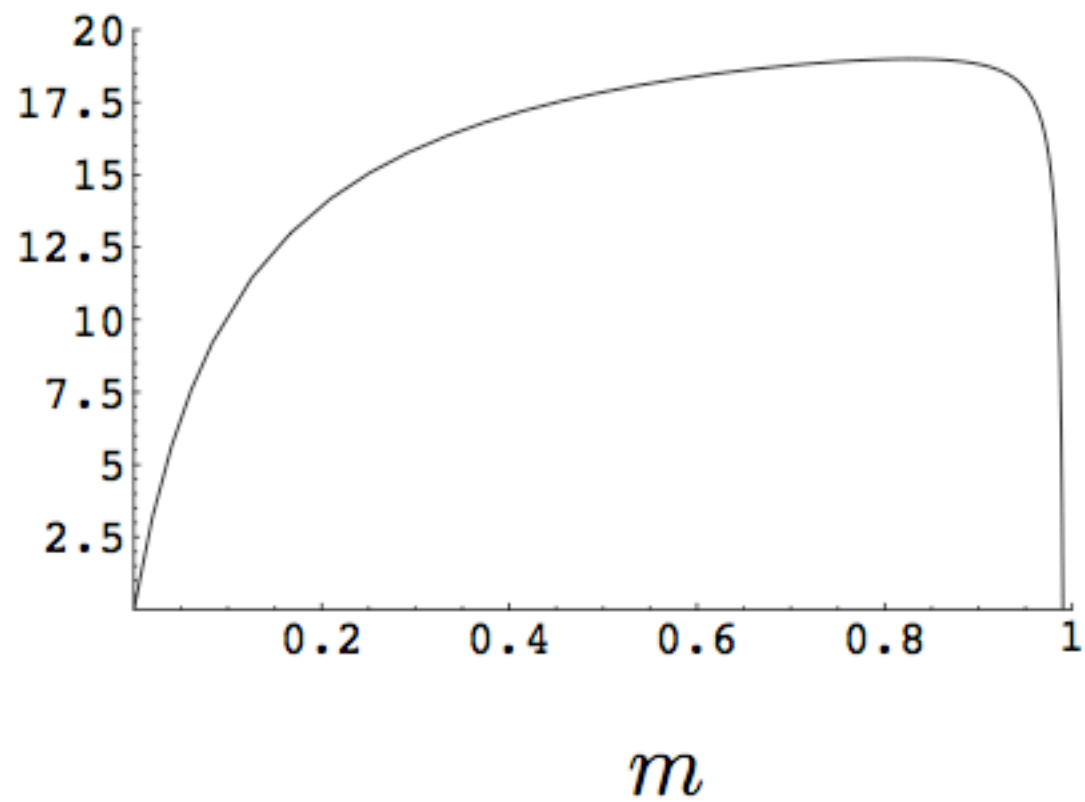


$\beta(\varphi)$  $\mu + \alpha(\varphi)$





$R_0(1, m)$



$R_0(1, m)$

