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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

1 Introduction

Most models for the evolution of parasite virulence assume that it is governed by a trade-off between transmission and parasite-induced mortality (Ewald, 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 level there *should* be a relationship between parasite reproduction and negative effects experienced by the host (otherwise we would hesitate to call the parasite a parasite), these negative effects are not necessarily expressed as additional mortality. Moreover, these negative effects, whatever they are, could depend on parasite exploitation and transmission strategies in a variety of ways (morbidity, anaemia, sterilisation).

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

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

mediate or high virulence for vector-borne diseases. For instance, for indirectly 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-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 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 transmission), he shows that, under some conditions, Ewald's (1983) predictions are verified. Finally, Gandon (2004) developed a general framework to 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 virulence (Gandon, 2004). Other models on vector-borne parasites usually involve malaria. Several models consider its within-host dynamics (for a review, see 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 epidemiological dynamics. To our knowledge, there have been no theoretical studies on the trade-off between transmission and virulence for malaria though studying the trade-off emergence for particular host parasite interactions might be crucial (Ebert and Bull, 2003).

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

notypical or genotypical variations among hosts and parasites are sufficient 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 combined with a larger-scale epidemiological model (for reviews, see Alizon and van Baalen, submitted; Mideo et al., submitted). Inspired by malaria, we therefore study an extension of our earlier model (Alizon and Van Baalen, 2005) in which parasites alternate between two host species. We also assume that parasites are able to reproduce in both hosts, which means we are focusing on biological transmission (as opposed to mechanical transmission where the vector only carries the parasite). We will often refer to malaria for illustrative purposes, but several parasites species could fit this model (for instance protozoa such as *Leishmania*).

About Plasmodium falciparum

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 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 very virulent disease as most infected adults recover from the disease or survive a relatively long time (Boyd, 1949). That is, the human host, at least the adults (children being much less immunised), does not seem to be an important component among the factors that constrain malaria evolution. The majority of deaths caused by malaria seems to be due to a naive immune system (World Health Organization, 2003). This would explain why malaria 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 malaria (Carter and Mendis, 2002).

The parasite life cycle alternates between two host types: mosquitoes of the genus *Anopheles* and humans. An infected mosquito injects sporozoites when biting a human. This asexual form gives birth to merozoites that undergo clonal reproduction within the red blood cells (RBC) of the human host. Sometimes, infected RBCs produce sexual forms, called gametocytes (male or 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 through a series of stages, settle in the salivary glands of the mosquito, which then becomes infective.

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

2 The model

2.1 Parasite Within-host Dynamics

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

and Van Baalen, 2005). An important modification is that we distinguish two within-host stages of parasites: a stage that can replicate within the host (comparable to merozoites, the asexual stage of *Plasmodium*) and a stage that can be transmitted (comparable to the gametocytes, the sexual life-stage of *Plasmodium* which can be taken up by mosquitoes). Their densities are 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 the former reproduces asexually, only the latter can be transmitted. Koella and Antia (1995) developed a similar model but for acute infections. The parasite within-host dynamics are described by the following two equations

$$\begin{aligned} \frac{d\,x_1}{d\,t} &= (\varphi\,(1-m) - \sigma_1\,y)\;x_1 \\ \frac{d\,x_2}{d\,t} &= \varphi\,m\,x_1 - \sigma_2\,y\,x_2 \end{aligned} \tag{1}$$

where φ is the parasite intrinsic per capita growth rate, σ_1 the killing rate of 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 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 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.

Considering the specific case of malaria, one could expect gametocytes (x_2) to be targeted by specific components of the immune system but empirical 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 ask why a framework for persistent infections can be applied to malaria. The

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

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 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 infections on the evolution of *Plasmodium* will be the subject of a future study.

2.2 Modelling the Immune System

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 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:

$$\frac{d\,y}{d\,t} = b + c_1\,x_1 + c_2\,x_2 - \delta\,y \tag{2}$$

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 lymphocyte production due to the sexual parasite and δ the lymphocyte mortality.

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

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

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 persists (Recker et al., 2004). Here we assume that persistence occurs and use a persistent infection framework.

2.3 Equilibrium densities

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

$$\begin{aligned}
\tilde{x_1}(\varphi, m) &= \frac{\sigma_2}{\sigma_1} \frac{(1-m)\,\delta\,\varphi - b\,\sigma_1}{c_2\,\sigma_1\,m - (1-m)\,c_1\,\sigma_2}\,(1-m) \\
\tilde{x_2}(\varphi, m) &= \frac{(1-m)\,\delta\,\varphi - b\,\sigma_1}{c_2\,\sigma_1\,m - (1-m)\,c_1\,\sigma_2}\,m \\
\tilde{y}(\varphi, m) &= \frac{1-m}{\sigma_1}\,\varphi
\end{aligned} \tag{3}$$

One might ask why we defined a within-host system at all if we restrict ourselves to equilibrium situations. The main reason is that equation 1 and 2 allow us to easily incorporate biological processes (parasite growth, conversion of asexual parasites into sexual parasites, destruction of the immune system). Without such a model, it would be impossible to assess how equilibrium densities should depend on the various parameters and variables. As underlined 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 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 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 for vector-borne parasites.

2.4 Epidemiological Dynamics

Parasite fitness

To determine whether a parasite can invade a population, epidemiologists use 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 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 recovery rate γ, the natural host mortality μ, the disease-induced mortality (or virulence) α and the density of susceptible host S,

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

For parasites that alternate between two hosts, the parasite's overall R_0 involves the two hosts. The strict alternation of the parasite's two hosts implies 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 h suffix to humans, we get

$$R_0 = \frac{\beta_{v\to h}}{\mu_v + \alpha_v + \gamma_v} S_v \cdot \frac{\beta_{h\to v}}{\mu_h + \alpha_h + \gamma_h} S_h \tag{5}$$

Here, we assume that the epidemiological parameters (virulence, transmission and recovery) in the vector are constant. This implies that the vector component of the R_0 is constant. All these assumptions are of course debatable 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 equilibrium more rapidly than the human population density, *i.e.* that S_v is constant.

Thus, the expression of the parasite's R_0 becomes

$$R_0 \propto \frac{\beta_{h\to v}}{\mu_h + \alpha_h + \nu_h} S_h \tag{6}$$

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

Parasite transmission rate

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 efficiency of transmission from humans to vector. As in Koella and Antia (1995) and following experimental data described in the Introduction, we link the equilibrium density of sexual parasites ($\tilde{x}_2$) and transmission from the main host to the vector ($\beta_{h\to v}$).

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

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 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 blood meal is Poisson-distributed:

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

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

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

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,

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

Assessing the number of sexual parasites required to establish an infection (n) is not simple. Here, for numerical calculations, we arbitrarily take $n = 40$ 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 A.

Parasite virulence

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

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

The main contribution to parasite virulence comes from the asexual life-stage because sexual parasites do not replicate. Note that according to this equation 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 parasite density (the first and second terms).

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

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

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

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 and its conversion rate m. Unfortunately, this function is too complex for a complete analysis but we still can develop a numerical ESS analysis.

Table 1 here

3 Results

3.1 An S-shaped Transmission Function

We find that the transmission rate (equation 8) has an S-shape both when it is 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 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 affects the φ value for which the saturation occurs.

figure 1 here

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

3.2 Emergence of a Trade-off Between Transmission and Virulence

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 parameter 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) is maximised. For low levels of virulence, transmission accelerates with virulence but it quickly levels of to a plateau value. Near the ESV the curve is strongly convex (figure 2A), which implies that here, contrary to our previous approach with a linear transmission function (Alizon and Van Baalen, 2005), small variations of φ may have an important effect on the R0 value of the parasite (figure 2B).

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 curve) than with the linear transmission function (dashed curve). Thus, the cost of expressing a virulence higher or lower than the optimum is huge.

figure 2 here

3.3 Parameter Influence on the Optimal Virulence

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, we can determine the evolutionary equilibrium (*i.e.* the optimal growth rate $\varphi^\star$ maximising R_0). This optimum can also be indicated by giving the optimal virulence and the optimal transmission ($\alpha(\varphi^\star)$ and $\beta(\varphi^\star)$) which is the

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

figure 3 here

Figure 3 presents a sensitivity analysis for the host natural mortality rate (μ) 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 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 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). Thus, parameter variation may not strongly affect the selection pressure.

3.4 The Optimal conversion rate

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

figure 4 here

When the parasite's reproductive success (R_0) is plotted as a function of m 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 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 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 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 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 unique optimal strategy: the strategy with high conversion rates (Appendix B). This makes sense because if sexual parasites are harmless and less targeted by the immune system, rapid conversion is a 'refuge' strategy (parasites colonise a niche without predators).

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. 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 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 (see Appendix C for further details). Thus, independently from the shape of the transmission function, our results suggest that the optimal conversion strategy will depend on the detrimental effects of clonal and sexual life-stages.

3.5 Consequences of Health Policies

Anti-parasite treatments are known to influence parasite resistance but some suggest they might affect other parasite life-history traits such as virulence as 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 Van Baalen, 2005; André and Gandon, 2006). Here, we study the evolutionary consequences of treatment strategies that differ in the parasite life-stage they 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 treatment targets sexual life-stages and we add an extra mortality term (τ_2) to x_2. Equation 1 is now

$$\begin{aligned} \frac{d\,x_1}{d\,t} &= (\varphi(1-m) - \sigma_1\,y - \tau_1)\;x_1 \\ \frac{d\,x_2}{d\,t} &= m\,\varphi\,x_1 - (\sigma_2\,y + \tau_2)\,x_2 \end{aligned} \tag{12}$$

where τ_1 and τ_2 are the intensities of the treatment.

In the short term, both these treatments reduce disease-induced mortality by decreasing parasite load. Not surprisingly, increasing the intensity of the treatment reduces the parasite's R_0 (figure 5). The treatment against the 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 on the parasite's fitness.

figure 5 here

To study the evolutionary consequences of treatment strategies, we assess how the parasite's within-host growth rate evolves in response to a particular 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 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 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 high enough to ensure a R_0 greater than 1 (figure 5A). For a treatment targeting the sexual parasite (figure 5B), increasing the growth rate may not be sufficient for the parasite to restore its R_0. It is important to note that treatments also affect the optimal conversion rate. For instance, extra-mortality of the asexual life-stage parasites may select for lower conversion rates, which partially counteracts the effectiveness of the treatment (figure not shown).

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

4 Discussion

Several studies have tried to work out from first principles the possible shapes of the trade-off between transmission and virulence (Alizon and van Baalen, submitted; Mideo et al., submitted). This study attempts to test the general 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

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

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

4.1 Transmission

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 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 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 only effectively convert a limited number of gametocytes into sporozoites; additional gametocytes ingested by a mosquito are thus essentially wasted.

Stochasticity in the number of parasites ingested by a mosquito may give rise to an accelerating relationship between density and infection success for low 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 transmission function, as assumed in some theoretical studies (Regoes et al., 2002), then emerges quite naturally from the underlying biological mechanisms.

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

4.2 A fixed value of optimal virulence

When the particular aspects of a vector-borne parasite are taken into account, a saturating trade-off results which yields a very robust evolutionary stable virulence (ESV) value. The precise mathematical definition of the virulence 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 transmission function (Alizon and Van Baalen, 2005). An interesting consequence is that when the transmission function levels off, high levels of virulence are 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 threshold increasing parasite density only increases virulence, very virulent strains are strongly counter-selected.

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 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 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 models with a linear transmission rate, *both* natural mortality and deleterious effect constants have strong effect on the ESV. Our study helps to identify the problems and potential shortcomings of trade-off theory when trying to predict optimal levels of virulence for specific cases.

4.3 Maturation or Growth?

Our study highlights the fundamental incompatibility of conversion and growth. One may find two distinct and locally stable equibria with similar reproductive success: in the first case parasites specialise in the production of asexual parasites (low conversion rate) while in the second parasites specialise in the production of sexual parasites (high conversion rate). This dilemma resembles 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 for the immune system to clear the clonal life-stage).

In the case of human malaria, many studies have tried to understand why the conversion rate is so low. Taylor and Read (1997) suggest two evolutionary explanations: either high gametocyte densities in a blood meal lead to 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

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

The best way to understand the optimal conversion rate is perhaps to interpret 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 outcompeted locally, which is often a problem given the high frequency of multiple infections (Read and Taylor, 2001). Thus, multiple infections could also act on the optimal conversion rate by favouring low maturation rate.

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

4.4 Which Life-stage to Target?

It has been shown recently that serial passages of *Plasmodium chabaudi* in immune mice select for increased levels of virulence (Mackinnon and Read, 2004a). Of course, in a serial passage experiment, transmission stages have very little importance in their experiment and it is the ability to colonise 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. Nevertheless, this experiment tends to confirm two of our results: treatment may select for higher levels of virulence and bypassing transmission stages might select for even higher levels of virulence.

More precisely, we find that treatments targeting the sexual part of the parasite'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 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 should target sexual parasites instead to reduce the parasite's reproductive success. Thus, there is a conflict between the optimum of the individual and that of the population, as noticed by several authors (Anderson and May, 1991; Van Baalen, 1998; Alizon and Van Baalen, 2005).

Our results raise some interesting points with respect to treatments targeting the transmission stages. In contrast to the study by Gandon et al. (2001), 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 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 Van Baalen, 2005). The second reason is that actively destroying transmission stages is not the same as 'blocking transmission'. In the former case, the treatment 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 feedback loop (for instance through multiple infections) that anti-transmission treatment may influence parasite virulence evolution.

Ironically, deciding which anti-parasite therapies to use might lead to a similar dilemma. One may develop an anti-transmission life-stage treatment, which 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 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 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 the short term the priority is to heal infected people, which means decreasing their parasitaemia by using treatments targeting merozoites. The problem is 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 infected hosts with preventive vaccination against gametocytes.

Conclusions

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

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

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

Our model indirectly addresses the question of malaria's low virulence by suggesting that virulence evolution could be driven mainly by the transmission function. However, we must add that several other factors have been proposed 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 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 no clear trade-off between transmission and host death rate. However, the sigmoid constraint function that emerges from our model leads to the same 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 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 to the one we studied here, also explicitly accounts for the possible sub-lethal effects. Another hypothesis to explore is host developmental heterogeneity: it 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 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

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Appendixes

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

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 successfully initiate an infection) does not qualitatively affect the results as we show on figure A.1 and A.2.

figure A.1 here

For different values of n the trade-off curve has the saturating shape already 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 dispersal stage is sexual) the curve is highly concave, which implies a stable evolutionary virulence.

figure A.2 here

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

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 in (McKenzie and Bossert, 1997). Thus, $u_2 = 0$. figure 4 is then different.

figure B.1 here

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 any harm to the main host, parasites should evolve towards high conversion rates.

C Case with a linear transmission rate

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

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

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

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. More precisely, what we are interested in is the consequences of deleterious effects of sexual parasites (u_2) on the optimal conversion rate.

figure C.1 here

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 variable if $u_2 > 0$. This result is similar to the result found with a sigmoid 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**
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.e.* infected host mortality du 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

740

Figure Captions

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 transmission is complicated and at high densities it saturates. Parameter values are $n = 40$, $c_1 = 0.1$, $c_2 = 0.01$, $\sigma_1 = 1$, $\sigma_2 = 0.1$, $b = 0.01$, $\delta = 1$, $a = 10$.

Fig .2: Trade-off curve (A) and basic reproduction ratio curve (B). Dashed 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 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 $w = 0.01$.

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. 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 $\mu = 0.1$, 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 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, 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.

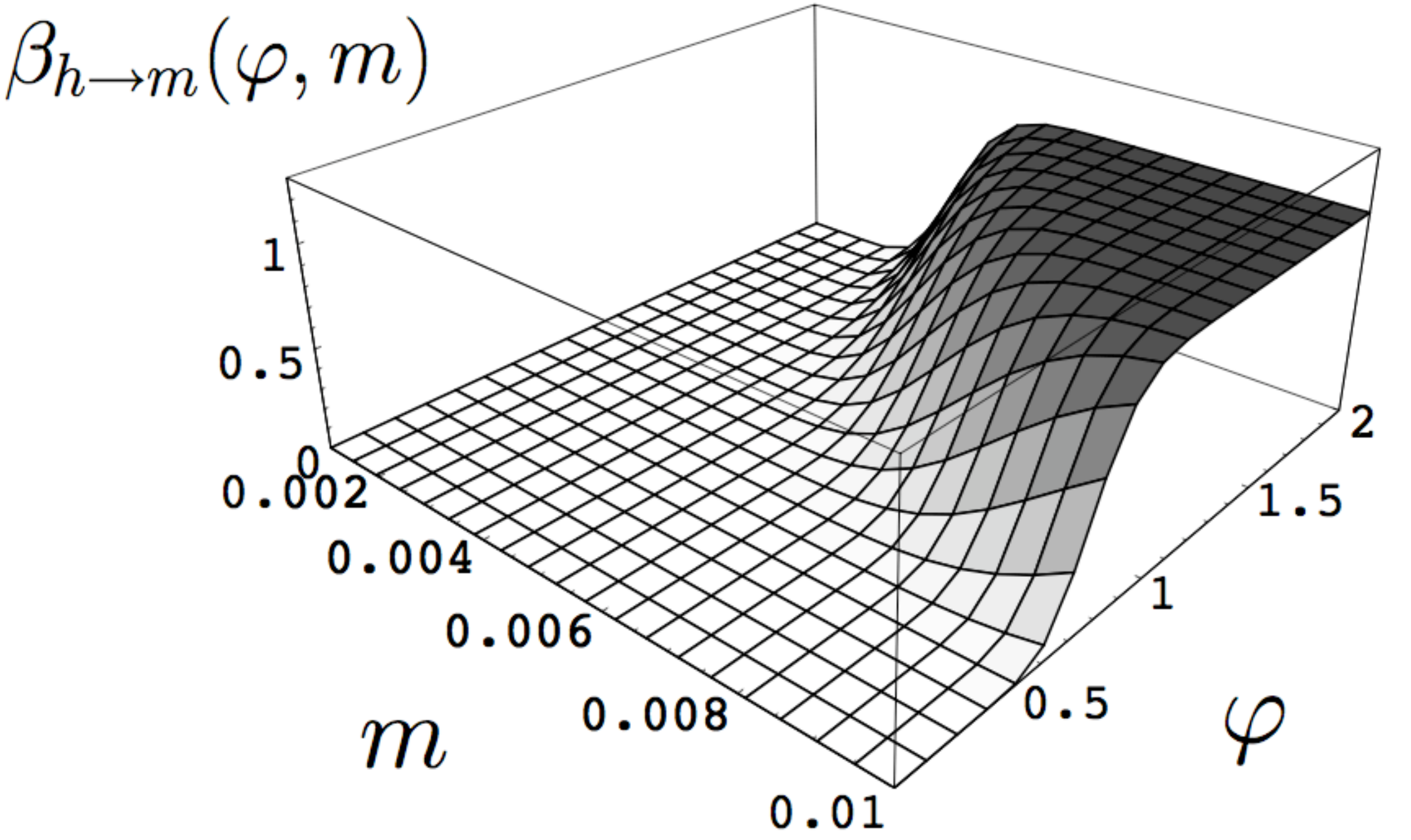
Fig. 5: Effect of a treatment targeting either the asexual (A) or the sexual life-stage (B). Grey colours indicate the value of the R_0 (the darker the area, the greater the R_0) depending on the intensity of the treatment and on the parasite growth rate (φ). The black and white dashed lines indicate the optimal value 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 figure 2.

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

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 details, see figure 4.

Fig. B.1: R_0 value depending on the parasite conversion rate (m) and within-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 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 effects and with a linear transmission function. Here, $\varphi = 1$ and other parameter values a identical to figure 2 except parameter a in figure B which has been rescaled ($a = 0.02$) to have similar maximum transmission value.


$\beta_{h\to m}(\varphi, m)$
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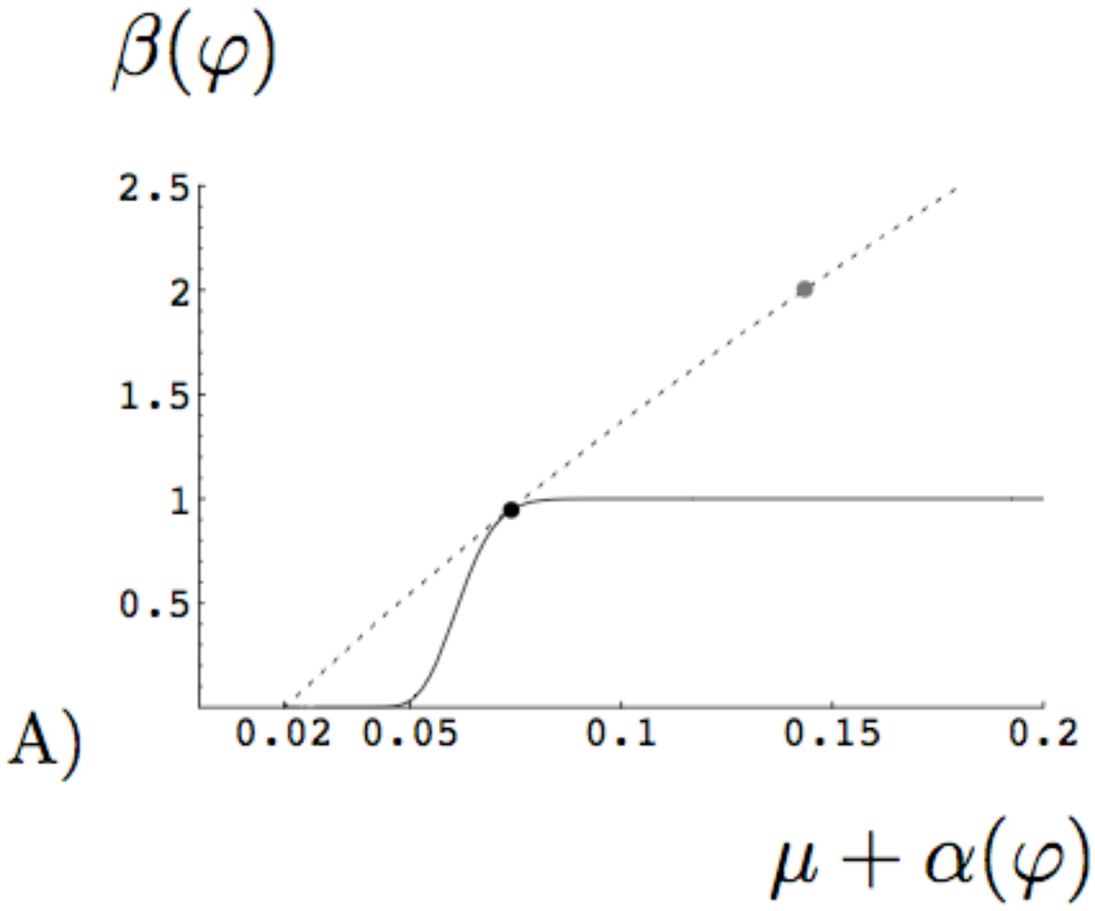
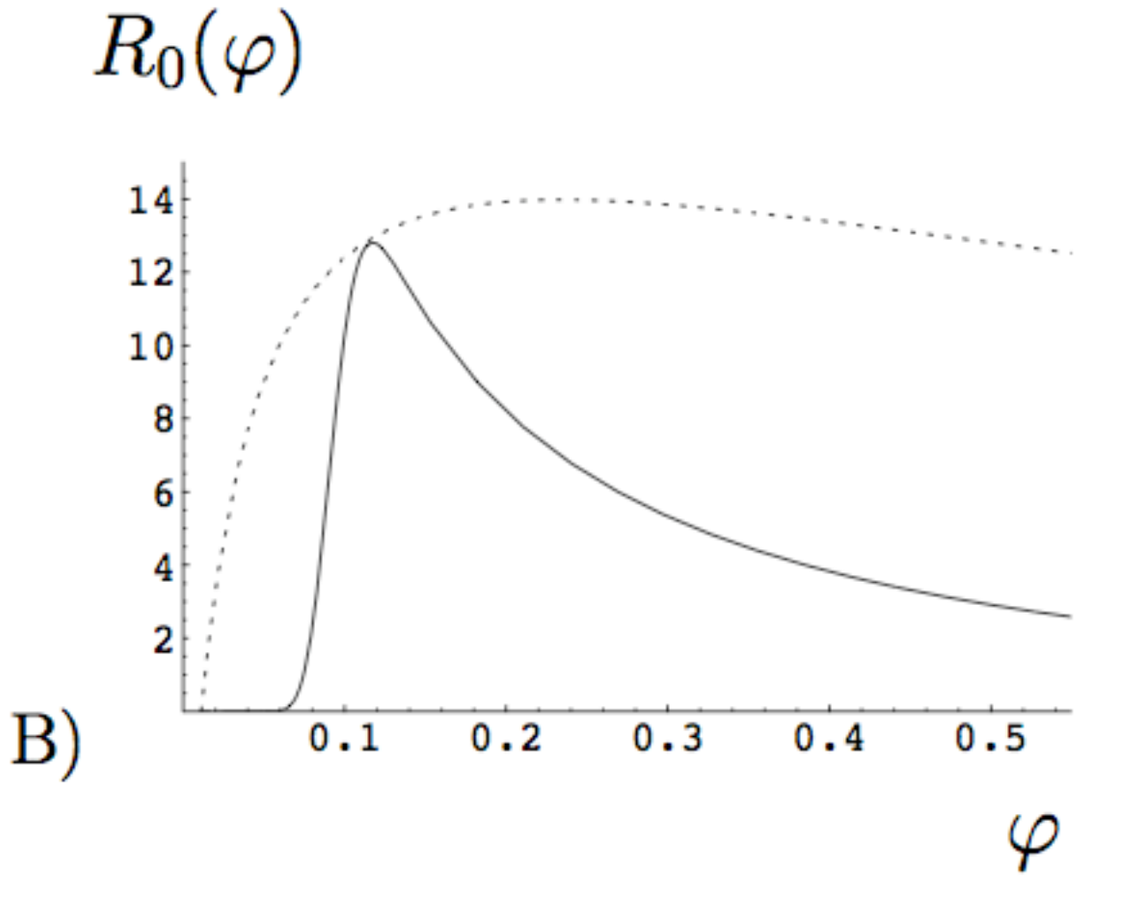
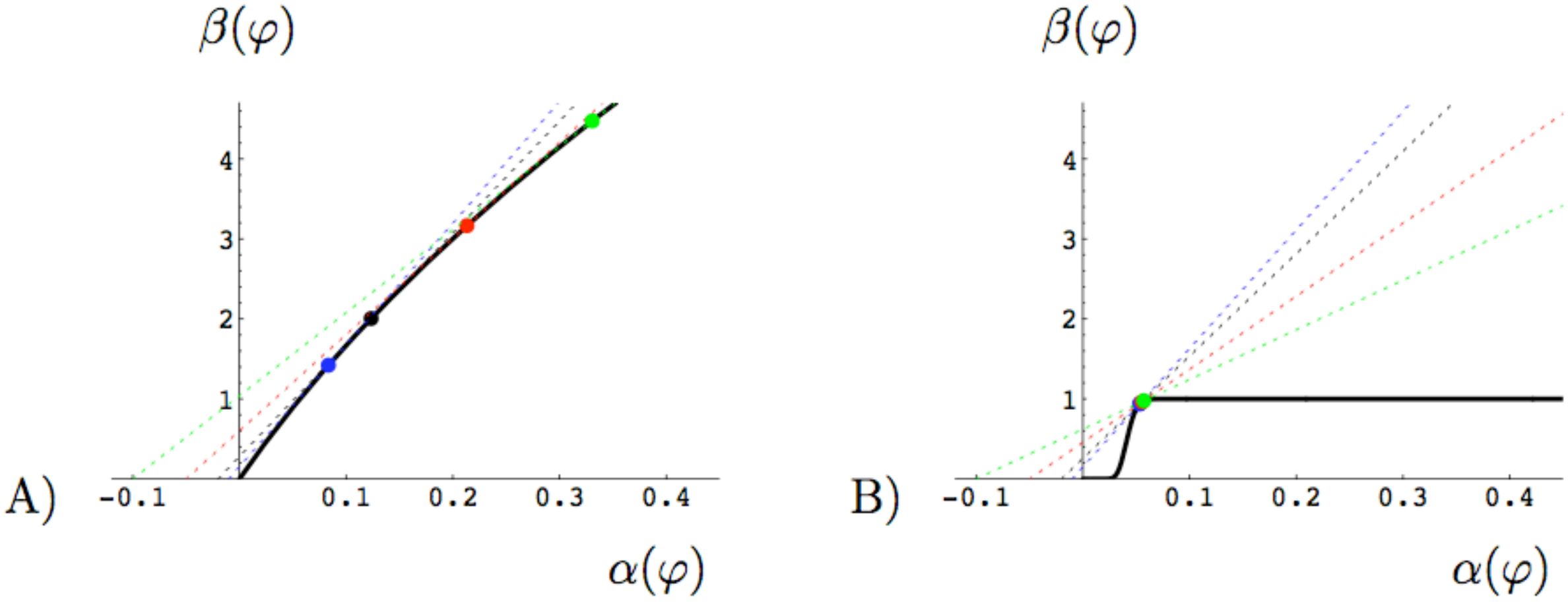
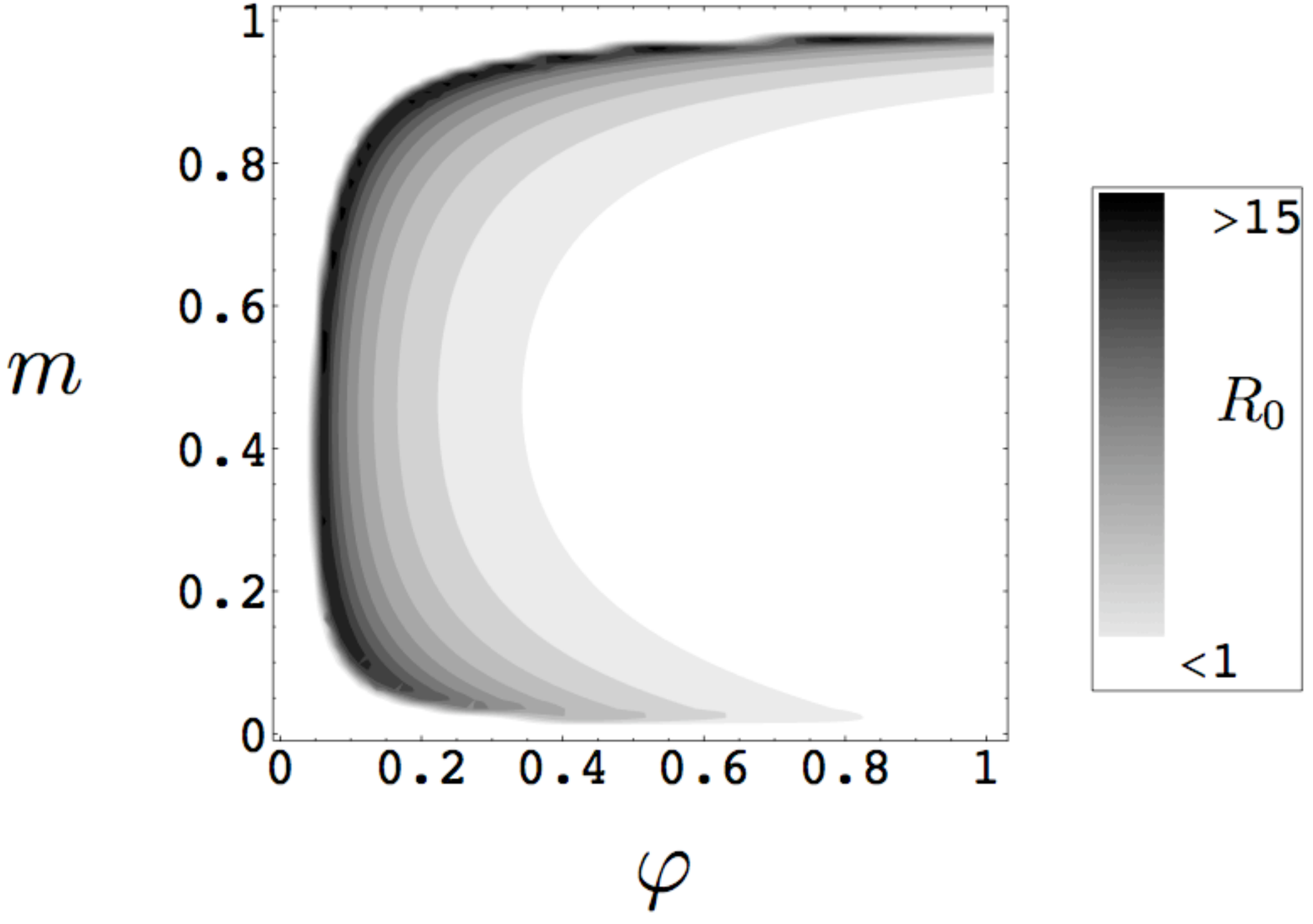
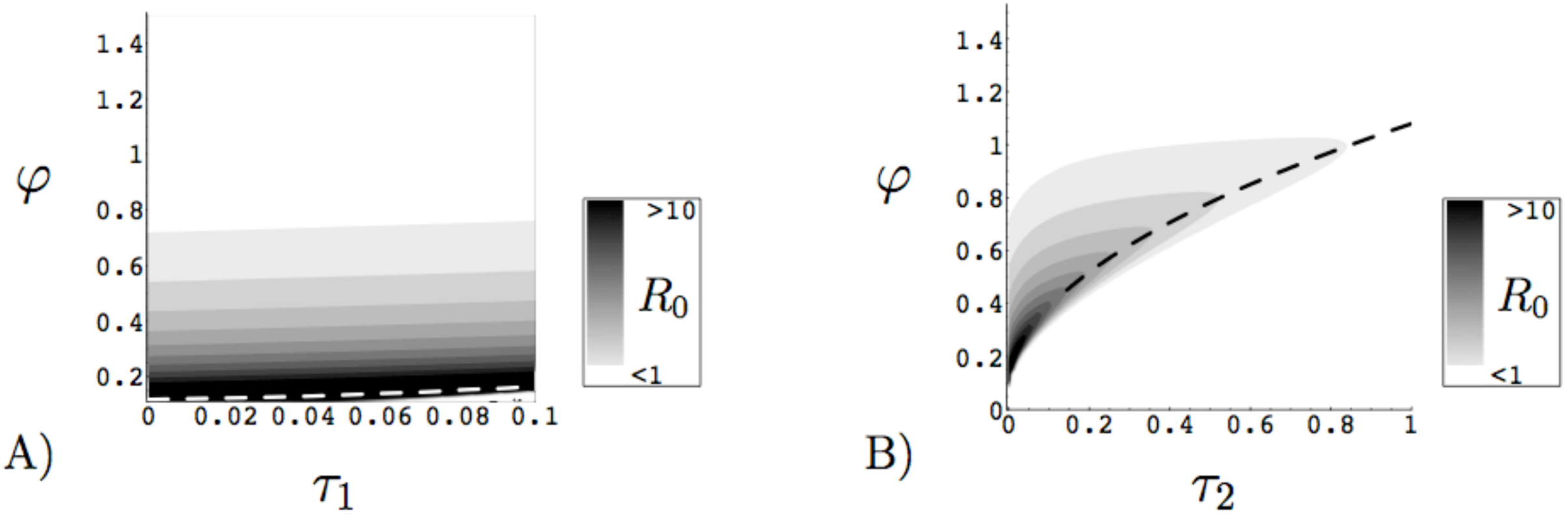
0.5
0
0.002
0.004
0.006
0.008
0.01
m
0.5
1
1.5
2
φ

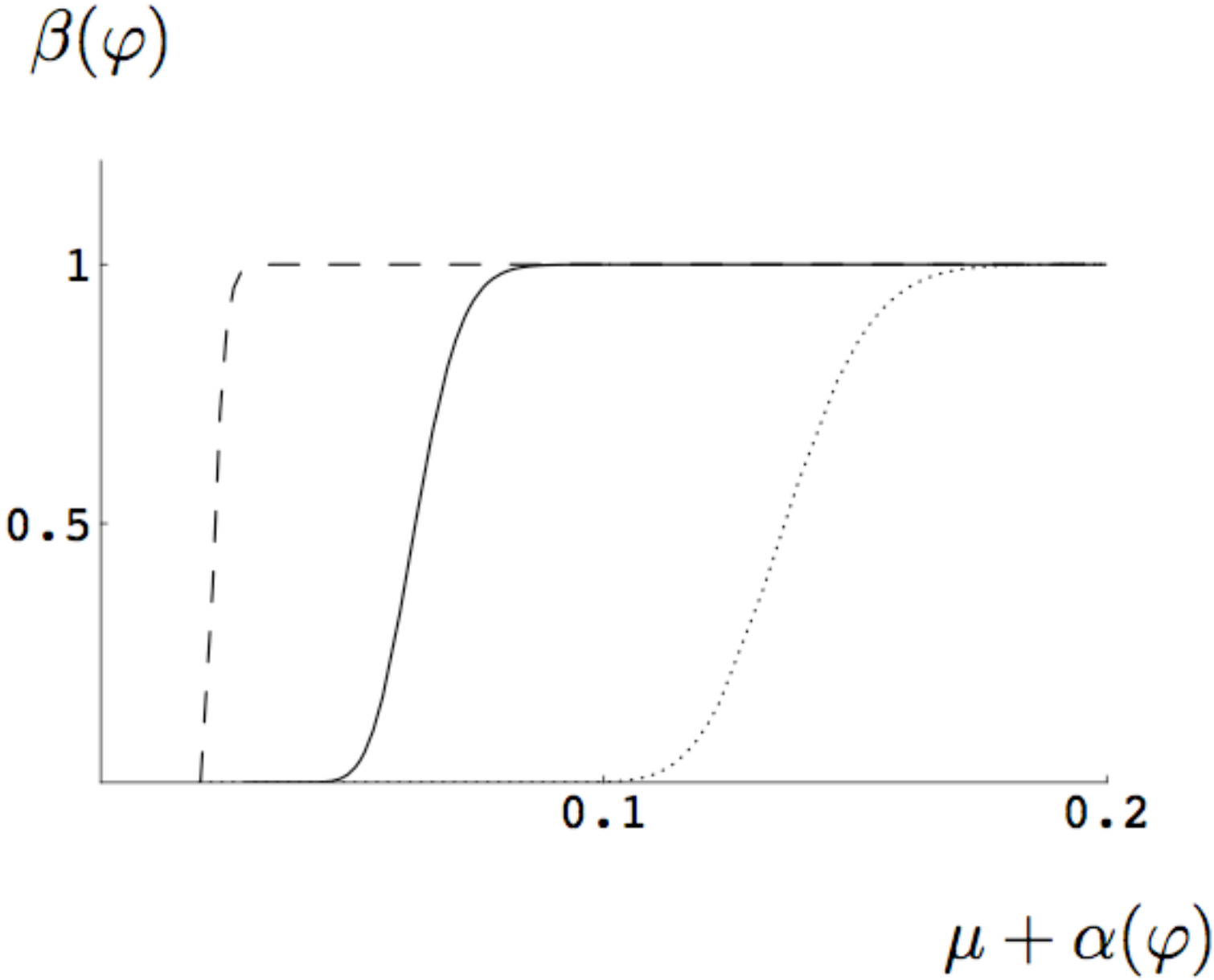

$\beta(\varphi)$
2.5
2
1.5
1
0.5
0.02
0.05
0.1
0.15
0.2
A)
$\mu + \alpha(\varphi)$

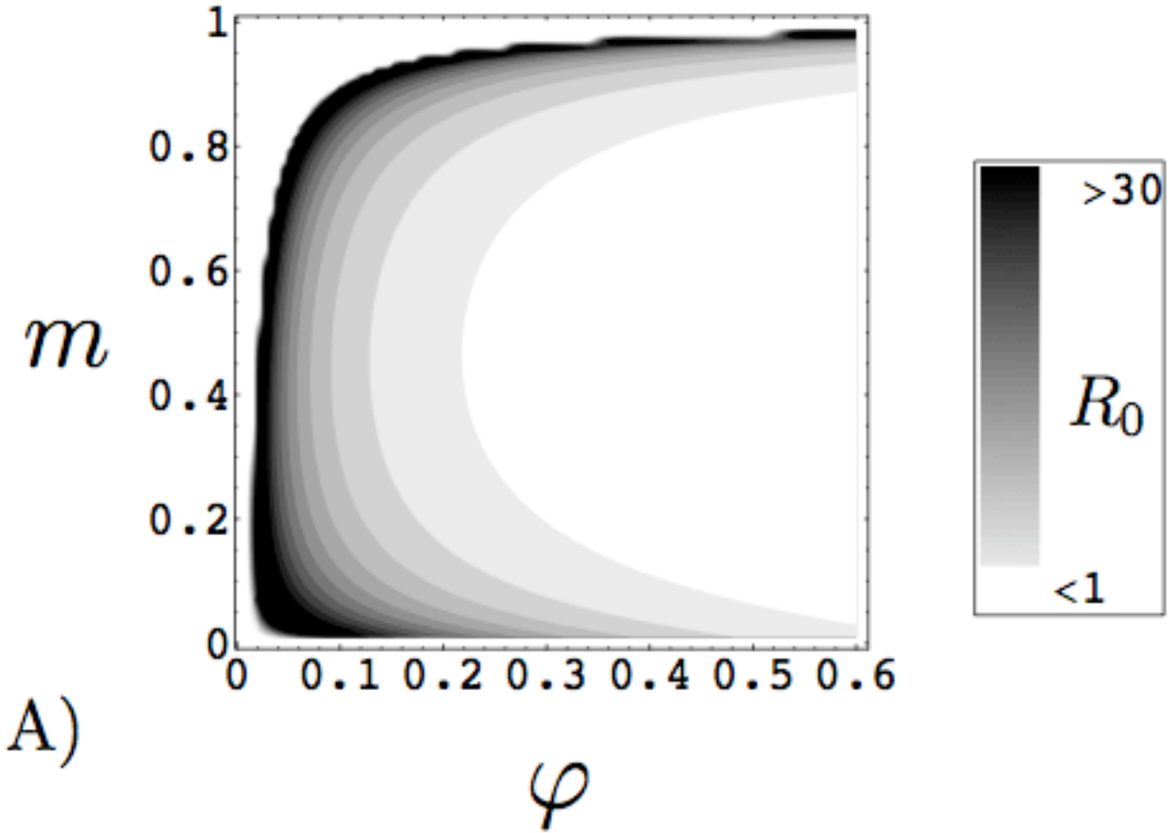

$R_0(\varphi)$
14
12
10
8
6
4
2
0.1
0.2
0.3
0.4
0.5
B)
φ

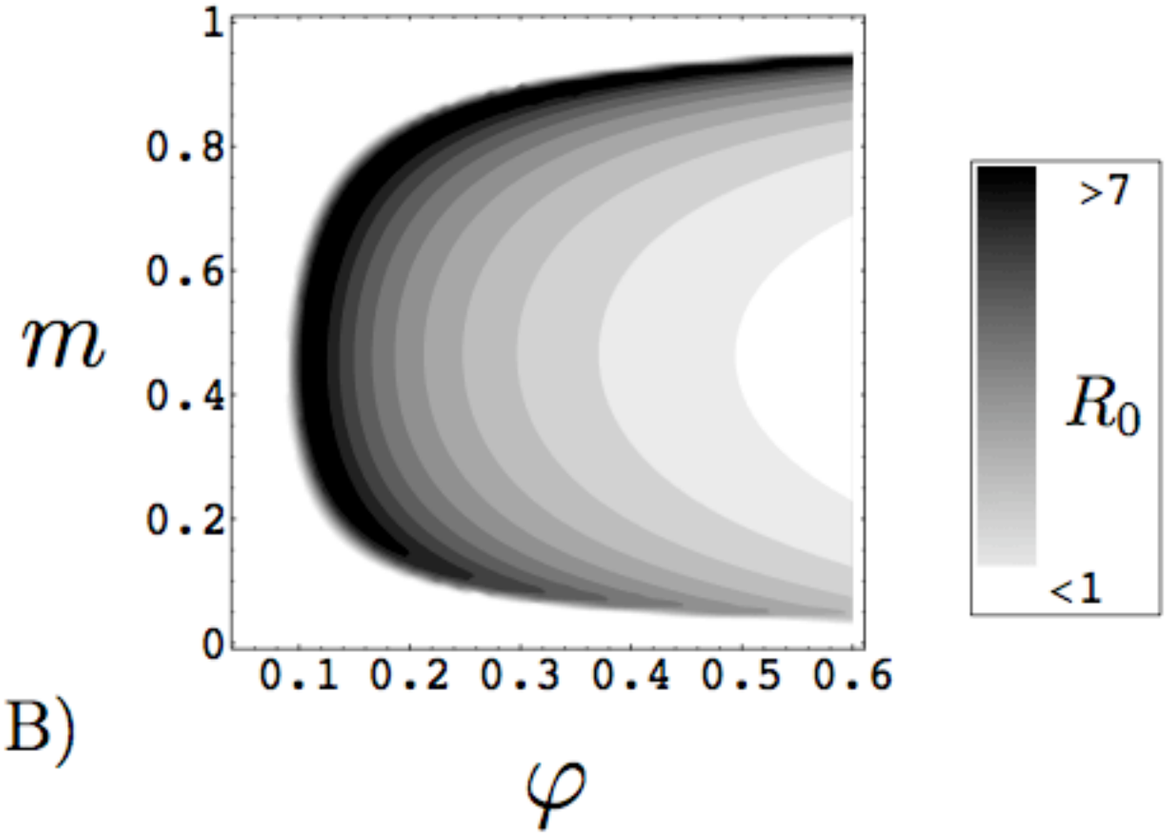

β(φ)
4
3
2
1
-0.1
0.1
0.2
0.3
0.4
α(φ)
A)
β(φ)
4
3
2
1
-0.1
0.1
0.2
0.3
0.4
α(φ)
B)


m
1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
φ
>15
R_0
<1


A)
φ
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.02
0.04
0.06
0.08
0.1
τ_1
>10
R_0
<1
B)
φ
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.2
0.4
0.6
0.8
1
τ_2
>10
R_0
<1


$\beta(\varphi)$
1
0.5
0.1
0.2
$\mu + \alpha(\varphi)$


1
0.8
0.6
0.4
0.2
0
0 0.1 0.2 0.3 0.4 0.5 0.6
m
φ
>30
R0
<1
A)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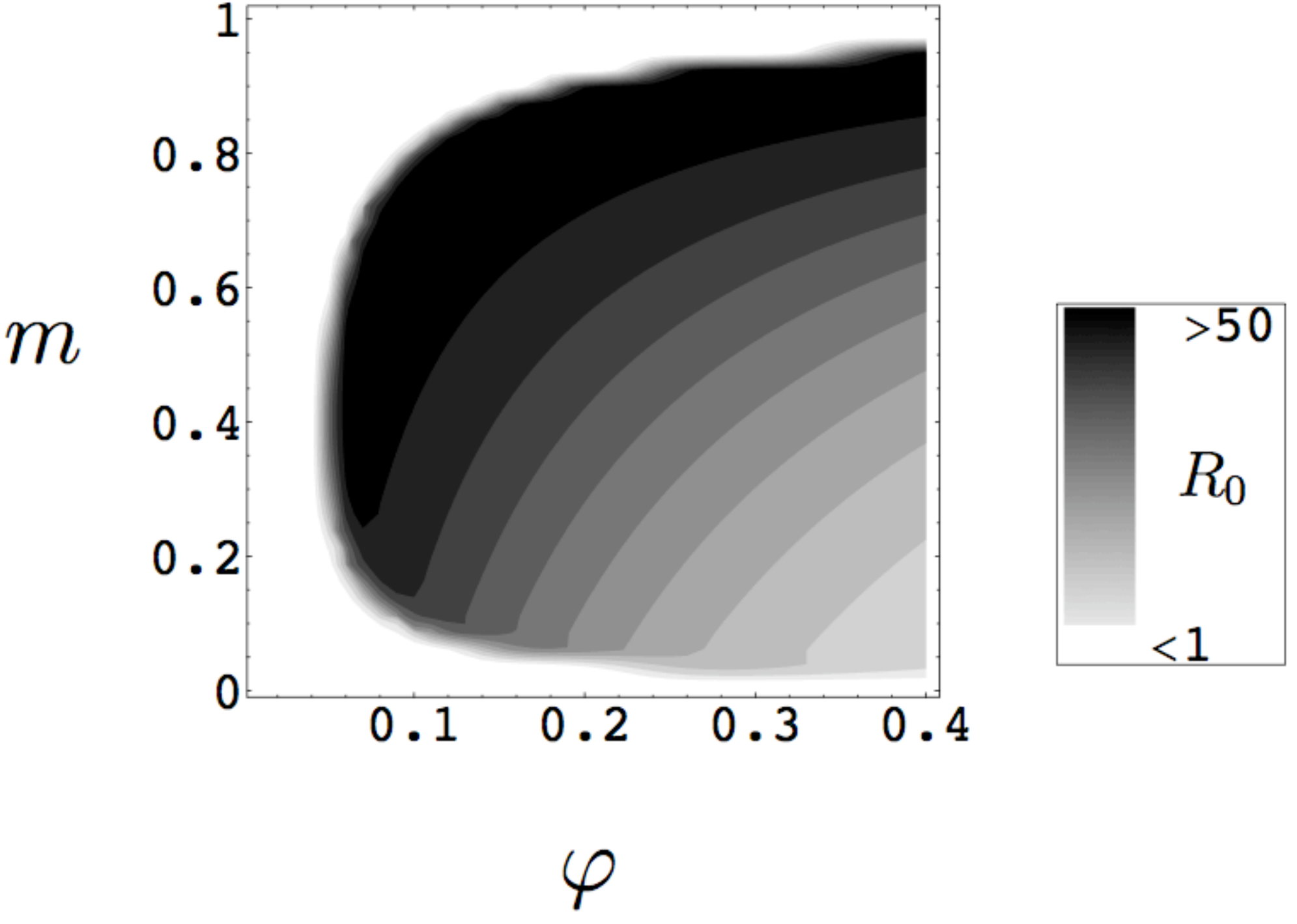
0.4
0.2
0
0.1 0.2 0.3 0.4 0.5 0.6
m
φ
>7
R0
<1
B)


m
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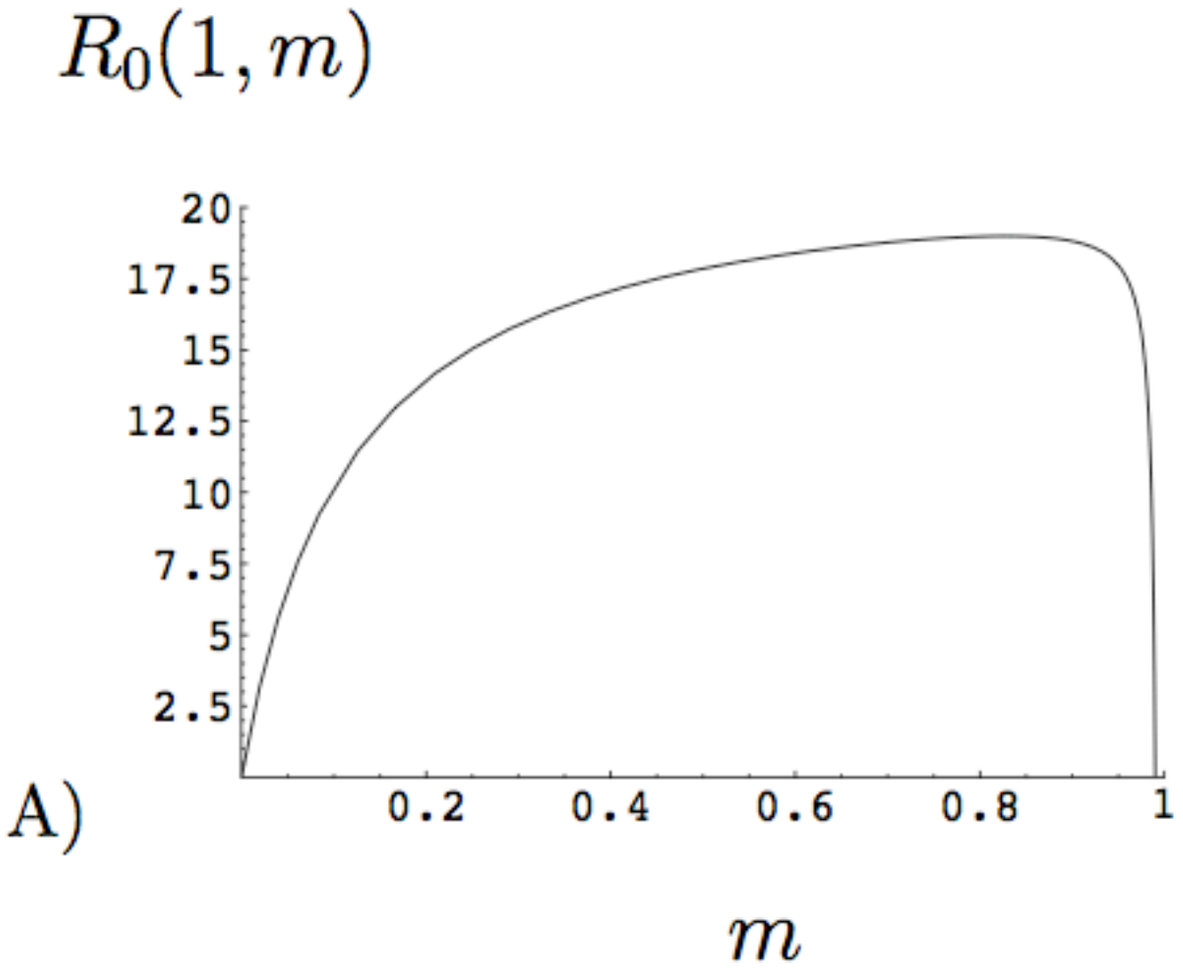
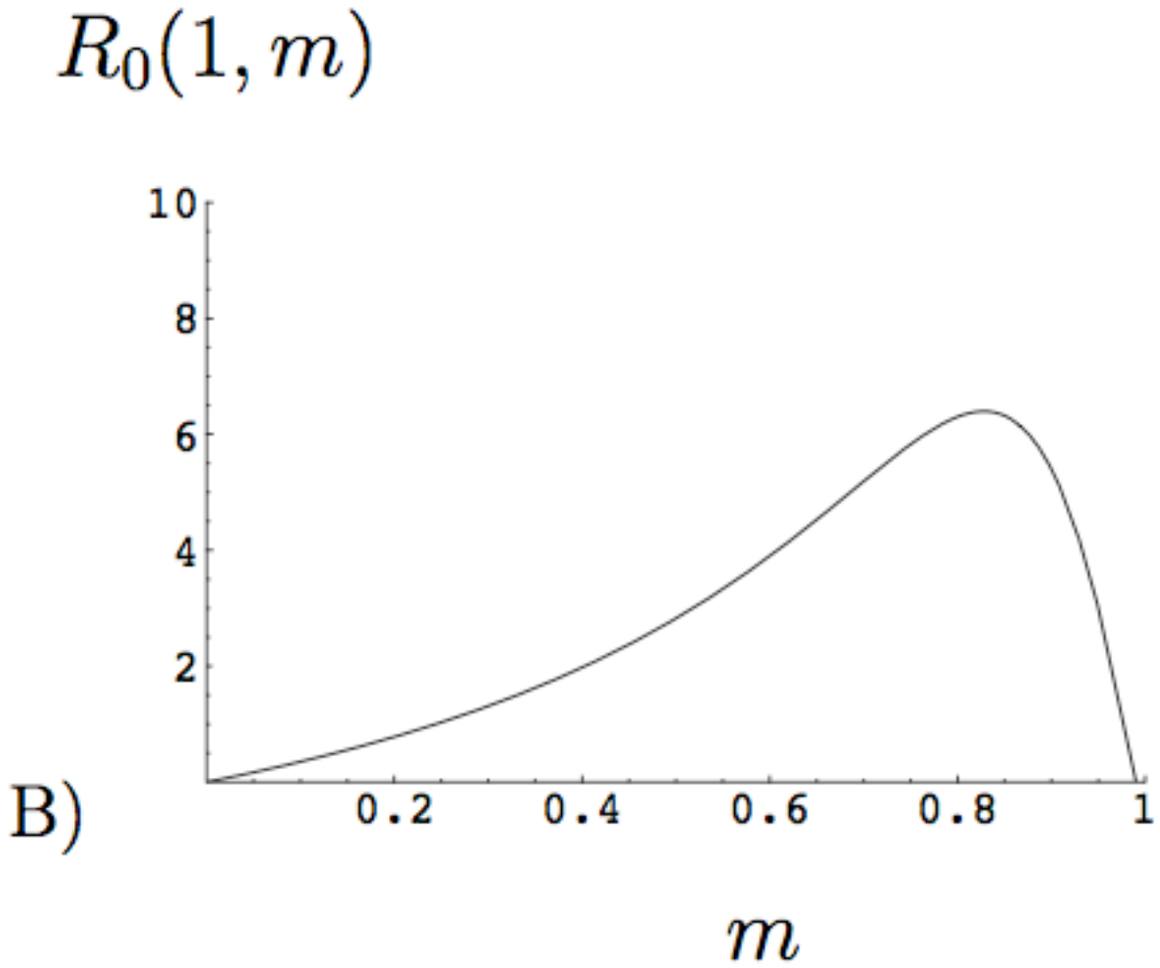
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4
φ
>50
R_0
<1


$R_0(1,m)$
20
17.5
15
12.5
10
7.5
5
2.5
0.2
0.4
0.6
0.8
1
m

A)


$R_0(1,m)$
10
8
6
4
2
0.2
0.4
0.6
0.8
1
m

B)