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Trois essais en bio-économie dynamique

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RÉSUMÉ

Cette thèse se compose de trois articles qui traitent de la dynamique économique de l'utilisation soit d'un antibiotique ayant comme objectif de combattre une infection bactériologique, soit d'un organisme génétiquement modifié ayant comme objectif de combattre une population de nuisibles. Nous nous intéressons au contexte particulier créé quand de tels instruments peuvent perdre leur efficacité à l'usage. Pour chacun de ces instruments, nous modélisons l'efficacité comme une ressource renouvelable et déterminons leur utilisation optimale comme solution d'un problème de contrôle optimal.

Dans le premier article, nous analysons l'exploitation d'un antibiotique dans un marché où les producteurs de cet antibiotique ont libre accès au stock commun d'efficacité de l'antibiotique et nous comparons l'équilibre qui en résulte à ce qui serait l'optimum social. La fonction de demande pour l'antibiotique est obtenue sous l'hypothèse que les individus diffèrent entre eux par rapport à leur valorisation d'être en bonne santé. La dynamique de l'efficacité de l'antibiotique est basée sur un modèle épidémiologique, qui décrit l'interaction dynamique entre le niveau d'efficacité et la population infectée. Il tient compte du fait qu'en raison de la sélection naturelle de bactéries résistantes, la consommation d'antibiotique pour combattre les infections tend à diminuer l'efficacité de l'antibiotique. Dans ce contexte, les producteurs d'antibiotiques ne s'intéressent qu'au stock courant de la population infectée, et au niveau courant de l'efficacité de l'antibiotique, ce qui détermine la volonté à payer pour le médicament de la part de la population malade. Ces producteurs entrent sur le marché jusqu'à ce que l'égalité du prix et du coût moyen soit atteinte. Quant à l'optimum social, la fonction d'objectif à maximiser tient compte du bien-être de la population totale, incluant la portion qui est en bonne santé ainsi que celle qui est infectée et qui ne consomme pas l'antibiotique. Cette maximisation tient aussi explicitement compte de l'effet du taux de traitement sur les niveaux futurs d'efficacité et de population infectée.

Nos résultats montrent qu'en fonction des paramètres du modèle, plus parti-

culièrement le coût de production et l'accroissement du taux de guérison attribuable au traitement, le niveau positif d'efficacité de l'antibiotique atteint à l'état stationnaire peut être plus élevé ou moins élevé que celui atteint en optimum social. Il existe même des configurations de paramètres pour lesquels les états stationnaires coïncident. Cependant, dans tous les cas, les sentiers menant vers ces états stationnaires en accès libre et à ceux en optimum social vont différer quant à la proportion de la population infectée qui reçoit un traitement.

Dans le deuxième article, nous caractérisons la politique de prix d'un monopoleur détenant un brevet d'une durée limitée. Nous supposons qu'à l'expiration du brevet le monopoleur devient un producteur concurrentiel parmi d'autres dans l'industrie de libre accès vendant une version générique de l'antibiotique initialement breveté. Afin de maximiser la valeur présente de ses profits, le monopoleur gère, via sa politique de prix, l'efficacité de l'antibiotique ainsi que le stock de la population infectée. Ces variables représentent respectivement la qualité de son produit et la taille de son marché. Nous montrons que le monopoleur tend à maintenir ces variables à un niveau plus élevé que le ferait un monopoleur myope, c'est-à-dire un monopoleur qui ne tiendrait pas compte des externalités dynamiques. Nous montrons également que sa politique de prix est caractérisée par une propriété dite de *turnpike* : le système approche l'état stationnaire qui serait atteint par un monopoleur bénéficiant d'un brevet d'une durée infinie et va rester dans le voisinage de cet état stationnaire pour une période plus ou moins longue selon la durée du brevet et les paramètres bio-économiques. À l'approche de l'expiration du brevet, le monopoleur se comporte de plus en plus comme un monopoleur myope, avec le résultat que son prix se mettra à décroître pour finalement atteindre celui du monopoleur myope au moment où le brevet prend fin. Dès que l'industrie du générique prend la relève, le prix chute subitement.

Dans le troisième article, nous étudions l'utilisation de semences génétiquement modifiées pour combattre une population nuisible. Nous nous servons d'un modèle entomologique qui inclut la diversité du pool génétique de la population nuisible, ainsi que le niveau même de la population. Une zone de refuge est utilisée en

tant qu'instrument pour contrôler l'évolution de la sensibilité du pool génétique de la population nuisible face aux semences génétiquement modifiées. Nous caractérisons la zone de refuge qui minimise la somme des coûts actualisés reliés aux dommages causés par la population nuisible ainsi qu'au coût supplémentaire des semences génétiquement modifiées. Le modèle est calibré pour le maïs *Bt* et le nuisible de la pyrale européenne. En raison de la linéarité de la fonction d'objectif, la zone de refuge consiste en des contrôles extrême et singulier. Pour les paramètres calibrés du modèle et des variations raisonnables, le bio-système tend vers un état stationnaire dans lequel la sensibilité des nuisibles est renouvelable. Cependant, si le contrôle est restreint à être invariant dans le temps, tel que proposé aux États-Unis, le système tend généralement vers un état stationnaire où la sensibilité est réduite à zéro. Dans une telle situation, des configurations de paramètres très particulières sont nécessaires pour que le bio-système tende vers un état stationnaire intérieur. Pour le modèle calibré, nous sommes en mesure d'estimer la réduction de coût que procure l'utilisation d'une zone de refuge variable plutôt qu'une zone de refuge invariable.

Mots-clés : économie de la résistance aux antibiotiques, gestion de la résistance des nuisibles, efficacité antibiotique, sensibilité du pool génétique, maïs *Bt*, ressource renouvelable, équilibre de libre accès, équilibre monopolistique, optimum social, contrôles extrêmes.

ABSTRACT

This dissertation is composed of three essays dealing with the economic dynamics of either the use of an antibiotic to combat bacterial infection or the use of a genetically modified crop to combat pests, when the efficacy of those instruments may decline with use. In each case, we model the efficacy variable as a renewable resource and its optimal use is determined as the solution of an optimal control problem.

In the first essay, we analyze the exploitation of an antibiotic in a market subject to open access on the part of antibiotic producers to the common pool of antibiotic efficacy and compare it to the social optimum. Demand for the antibiotic is derived under the assumption that individuals differ with respect to their valuation of being in good health. The dynamics of the antibiotic efficacy is based on an epidemiological model which describes the dynamic interaction between the level of efficacy of the antibiotic and the level of infection in the population, including the fact that antibiotic consumption tends to deplete the efficacy of the antibiotic in combating bacterial infections as the bacteria develop resistance to the antibiotic. The antibiotic producers care only about the variables that affect the instantaneous demand for the drug, namely the current stock of infected population and the current level of efficacy of the antibiotic, and enter the market until price is driven down to average cost. The social optimum, on the other hand, takes into account the welfare of the entire population, including that portion of the population which is in good health and that which is infected but chooses not to consume the antibiotic, as well as the effect of the current treatment rate on the future efficacy of the treatment and the future stock of infected population.

We show that depending on the parameters of the model, in particular the cost of production and the improvement in the recovery rate that results from treatment, the positive steady-state level of antibiotic efficacy to which the system tends under open access can be lower or higher than the level which should prevail in the socially optimal steady state. In fact there are parameter configurations for

which the steady states can be exactly the same. But no matter how the steady states compare, the socially optimal and the open-access paths to steady state will differ and involve different paths for the treatment rates.

In the second essay, we characterize the pricing policy of a monopolist who is protected by a patent for a finite period of time. We assume that once the patent expires, the monopolist becomes a competitive producer in the open-access industry which sells the generic version of the initially patented antibiotic. In order to maximize his inter-temporal profits, the monopolist manages, via his pricing policy, the levels of antibiotic efficacy and of the infected population. These can be viewed, respectively, as the quality of his product and his market size. We show that he tends to maintain a higher level of efficacy and a higher level of infected population than a hypothetically myopic monopolist who does not take into account the dynamic externalities. We also show that his pricing policy is characterized by a *turnpike* property. This means that the system approaches the steady state that would be reached by an infinitely-lived monopolist and remains in its neighborhood for a period of time, the length of which depends on the length of the patent life and on the bio-economic parameters. As the patent is about to expire, the monopolist begins to behave more and more myopically, leading to a continuous decrease in price until it finally reaches the price charged by a myopic monopolist. As soon as the open-access generic industry takes over, a discontinuous fall in price occurs.

Finally, in the third essay, we consider the use of a genetically modified crop to fight a pest population that feeds on the crop. We use an entomological model that captures the diversity of the pest population's gene pool, as well as the level of pest invasion itself. A refuge area is used as an instrument to control the evolution of the susceptibility of the pest's gene pool to the genetically modified crop. We characterize the refuge area that minimizes the sum of discounted costs related to the crop damage caused by the pest as well as the supplemental cost of the genetically modified crop. The model is calibrated for the use of *Bt*-corn to fight the European corn borer. Because of the linearity of the objective function, the

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optimal refuge consists of a bang-bang and a singular control. For the calibrated parameters, as well as reasonable variations of them, the bio-economic system tends to an interior steady state where the level of pest-susceptibility is renewable. However, when the control is restricted to being constant over time, as is currently done in the United States, the system generally tends to a steady state where the susceptibility is completely exhausted. In that case, it takes very particular parameter constellations for the system to reach an interior steady state. We are able to assess, for the calibrated model, the cost reduction attained by using a refuge area that varies over time instead of a time-invariant one.

Keywords: economics of antibiotic resistance, pest resistance management, antibiotic efficacy, gene pool susceptibility, *Bt*-corn, renewable resource, open-access equilibrium, monopoly pricing, social optimum, bang-bang control.

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INTRODUCTION

La capacité à combattre les maladies infectieuses et les pertes de récoltes dues aux insectes nuisibles ont connu un progrès rapide au cours du XX^{e} siècle. Avec la découverte du premier antibiotique, la pénicilline, par Alexander Fleming en 1928, et le développement successif d'une grande gamme d'antibiotiques d'une part, et d'anti-viraux d'autre part, nous nous sommes dotés de puissants moyens qui ont permis de contrôler et de guérir une multitude de maladies infectueuses. L'utilisation de pesticides, ainsi que d'organismes génétiquement modifiés (OGM) introduits plus récemment, ont permis de leur côté de minimiser considérablement les pertes de récoltes.

Il est cependant généralement admis aujourd'hui que ces moyens risquent de perdre – si ce n'est déjà fait – la totalité ou au moins une partie de leur efficacité. Cette perte est due à la croissance de la résistance des bactéries et des insectes nuisibles une fois qu'ils ont été en contact avec l'outil destiné à les combattre. La résistance d'organismes peut être causée par plusieurs mécanismes, dont la sélection naturelle d'organismes résistants. En effet, ce ne sont que les organismes sensibles à un traitement qui peuvent être combattu. Les organismes naturellement résistants profitent alors d'un avantage comparatif et peuvent devenir prépondérants dans le système biologique.

La perte d'efficacité de plusieurs traitements a pu être comblé dans le passé en partie pas de nouvelles innovations. Mais rien ne garantit qu'il sera ainsi dans le futur. La gestion de l'efficacité de ces traitements devient alors un enjeu socio-économique.

En premier lieu, les intervenants, soit les patients, médecins, pharmaciens et entreprises pharmaceutiques, soit les agriculteurs et entreprises productrices de semences OGM et de pesticides, n'ont pas les mêmes objectifs. Ils ne tiennent pas toujours compte de l'impact qu'ont leurs décisions sur leur environnement présent et futur. À titre d'exemple, il sera toujours avantageux pour un malade de prendre un antibiotique si celui-ci lui permet d'augmenter ses chances de guérison. Même

si le malade peut évaluer correctement l'impact espéré de la prise de l'antibiotique, c'est-à-dire son éventuelle guérison, il néglige les coûts associés à la résistance à laquelle feront potentiellement face les générations futures. Pour le malade, il s'agit seulement d'une dose d'antibiotique comparée à des milliers de doses prescrites au même moment à travers le monde. Du côté des entreprises, une fois le brevet échu, la formule biologique de l'antibiotique devient propriété intellectuelle commune et l'antibiotique peut être vendu sous forme générique. Les entreprises pharmaceutiques qui opèrent dans une industrie générique, quant à elles, ne prendront pas en considération que la vente accrue d'un antibiotique le rend inefficace dans le futur. Elles n'ont aucune incitation à maintenir le niveau d'efficacité de traitement élevé, car elles risquent de ne pas retirer le fruit de ce sacrifice étant donné que toutes les autres entreprises ont libre accès à ce stock d'efficacité.

Cet exemple illustre le fait qu'il existe plusieurs externalités, tant au niveau des utilisateurs de traitements qu'au niveau des producteurs. L'analyse de ces externalités et de leur impact sur l'évolution de l'efficacité des traitements, et l'éventuelle correction de ces externalités est du domaine de l'économie.

La problématique de la résistance a donné naissance à une littérature grandissante reliant des modèles économiques à des modèles biologiques plus ou moins stylisés. Une première contribution qui traite de la résistance aux antibiotiques et qui utilise un modèle épidémiologique est due à Brown et Layton (1996). Les auteurs modélisent la résistance comme une externalité dynamique entre l'utilisation qui en est faite pour combattre des maladies humaines et l'utilisation faite dans l'élevage animal.[1] Laxminarayan et Brown (2001) considèrent l'utilisation optimale de deux antibiotiques dont l'efficacité représente respectivement une ressource non-renouvelable. Cette utilisation dépend de la vitesse de réduction de l'efficacité ainsi que du coût de traitement de chaque antibiotique. Modélisant l'efficacité de l'antibiotique comme une ressource renouvelable, Wilen et Msangi (2003) montrent qu'un antibiotique devrait être utilisé à long terme d'un point de vue social de sorte

[1]Suivant la même idée, Laxminarayan (2002) analyse la couverture optimale d'un brevet attribué à un antibiotique qui peut être utilisé pour guérir des maladies humaines ainsi qu'animales.

à ce que l'efficacité de l'antibiotique se renouvelle.[2]

Quelques travaux considèrent l'évolution de l'efficacité de l'antibiotique dans un cadre de marché. Tisdell (1982) figure parmi les premières contributions sur ce sujet. Dans le cadre d'un modèle très stylisé à deux périodes, il soutient qu'un monopole peut corriger pour l'exploitation sous-optimale de l'efficacité de traitement d'antibiotiques ou d'insecticides qui en serait faite de la part d'une industrie concurrentielle. Fischer and Laxminarayan (2004) considèrent l'exploitation séquentielle d'antibiotiques par un monopole. En fonction du nombre d'antibiotiques à découvrir, un monopole exploite la séquence d'antibiotiques d'une manière trop, ou pas assez rapidement d'un point de vue social, selon le cas. Dans le cadre d'un modèle biologique stylisé, Mechoulan (2007) montre qu'une structure de monopole, suivie de la concurrence peut partiellement corriger pour le problème de la résistance aux antibiotiques.

Quant aux insectes nuisibles, plusieurs travaux traitent de la résistance aux pesticides et aux semences OGM. Hueth et Regev (1974) figurent parmi les premiers à développer un cadre bio-économique traitant de la résistance aux pesticides. Ils modélisent la sensibilité des insectes comme une ressource non-renouvelable et montrent que le coût associé à l'utilisation individuelle de la sensibilité est zéro, tandis que le coût social de remplacer le pesticide peut être extrêmement élevé. Munro (1997) analyse l'effet de l'utilisation myope et non-myope de pesticides sur l'évolution du bio-système.

La résistance aux OGM de la part d'insectes nuisibles a été le sujet de plusieurs travaux. La stratégie servant à contrôler pour la montée de résistance fait intervenir une zone de refuge, dans laquelle des semences naturelles sont cultivées. Une contribution importante est Hurley *et al.* (2001), qui présentent un modèle calibré

[2]L'efficacité de traitement d'un antibiotique est intimement lié à la problématique générale des infections transmissibles, qui a été l'objet d'étude de plusieurs travaux économiques. Pour en citer que deux à ce sujet, Gersovitz et Hammer (2004) comparent des efforts individuels de prévention et de guérison à ce qui serait socialement optimal dans le contexte d'un modèle général emprunté à l'épidémiologie. Philipson (2000) présente une revue d'articles, notamment traitant du SIDA.

pour la résistance de la pyrale du maïs. Dans un modèle à horizon fini, les auteurs analysent différentes tailles d'une zone refuge invariable dans le temps, et leur impact sur les coûts liés à la perte de récolte.

Cette thèse suit l'approche de proposer un modèle combiné bio-économique, qui permet l'analyse de l'efficacité de deux outils différents. Les deux premiers essais de cette thèse analysent l'efficacité de traitement d'un antibiotique sous différentes formes d'industrie. L'optimum social est également caractérisé. Le troisième essai analyse la résistance d'une espèce d'insectes auprès d'une semence OGM, plus particulièrement du maïs *Bt* (*Bacillus thuringiensis*). Les modèles biologiques présentés respectivement sont empruntés à l'épidémiologie et à l'entomologie, et permettent de modéliser l'efficacité de traitement de l'antibiotique ainsi que la susceptibilité du pool génétique d'insectes comme une ressource naturelle renouvelable. Pour traiter des problèmes de maximisation dynamique, nous avons recours au principe du maximum. La solution est présentée à l'aide de simulation numériques.

Dans le premier essai, nous analysons l'exploitation de l'efficacité d'un antibiotique dans un marché où les producteurs de cet antibiotique ont libre accès au stock commun d'efficacité de l'antibiotique et nous comparons l'équilibre qui en résulte à l'optimum social. La fonction de demande pour l'antibiotique est dérivée sous l'hypothèse que les individus diffèrent par rapport à leur valorisation d'être en bonne santé. L'efficacité de l'antibiotique est modélisée comme une ressource naturelle renouvelable exploitée en accès libre. La dynamique de l'efficacité de l'antibiotique est basée sur un modèle épidémiologique, qui décrit l'interaction dynamique entre le niveau d'efficacité et la population infectée. Il tient compte du fait que la consommation d'antibiotique dans le but de combattre les infections tend à décroître l'efficacité de l'antibiotique, en raison de la sélection naturelle de bactéries résistantes. Dans ce contexte, les producteurs d'antibiotiques ne s'intéressent qu'au stock courant de la population infectée, ce qui détermine la taille de leur marché, et au niveau courant de l'efficacité de l'antibiotique, ce qui détermine la volonté à payer pour le médicament de la population malade. Ces producteurs entrent sur le marché jusqu'à ce que l'égalité du prix et du coût moyen soit atteinte.

Quant à l'optimum social, la fonction d'objectif à maximiser tient compte du bien-être de la population totale, incluant la portion qui est en bonne santé ainsi que celle qui est infectée et qui ne consomme pas l'antibiotique. Cette maximisation tient aussi explicitement compte de l'effet de la population actuelle traitée sur les niveaux futurs d'efficacité et de population infectée. Nos résultats montrent que dépendant des paramètres du modèle, plus particulièrement le coût de production et l'accroissement du taux de guérison dû au traitement d'antibiotique, le niveau positif d'efficacité de l'antibiotique atteint à l'état stationnaire en accès libre peut être plus élevé ou moins élevé que celui atteint en optimum social. Il existe même des configurations de paramètres pour lesquels les états stationnaires coïncident. Cependant, dans tous les cas, les sentiers menant vers ces états stationnaires en accès libre ainsi qu'en optimum social vont différer quant à la production de la population infectée qui reçoit un traitement.

Le deuxième essai complète le premier dans la mesure que nous y présentons l'exploitation de l'efficacité de la part d'une firme monopolistique bénéficiant d'un brevet d'une durée finie. À l'encontre de l'industrie générique, cette firme tient compte des effets qu'a la fixation du prix de l'antibiotique sur le niveau futur de l'efficacité de traitement et de la population infectée. Afin de caractériser la politique de prix du monopole, nous envisageons deux points de référence: le monopole myope et le monopole bénéficiant d'un brevet de durée infinie. Nous montrons que le système dynamique est caractérisé par la propriété de *turnpike*: le système s'approche de l'état stationnaire qui serait atteint si la firme bénéficiait indéfiniment de sa situation de monopole et y demeure pour un certain intervalle de temps, lequel dépend de la durée du brevet. Le monopole devient plus myope vers la fin de vie du brevet et se comporte de manière parfaitement myope au moment de son expiration. Ceci est dû au fait qu'une fois le brevet échu, ses profits économiques seront nuls dans une industrie générique. Comme il attribue de moins en moins de valeur à l'efficacité de l'antibiotique et à la population infectée au fur et à mesure que le brevet approche de sa date d'expiration, le prix chargé par le monopole diminue, ce qui est accompagné d'une augmentation de la fraction de

population infectée qui reçoit le traitement. Ceci entraîne une diminution de la population infectée et, selon les paramètres du modèle, une diminution du niveau d'efficacité de l'antibiotique. Un saut vers le bas survient finalement dans le prix au moment où l'antibiotique passe aux mains de l'industrie générique.

Dans le troisième essai nous abordons la question de l'exploitation optimale de l'efficacité d'une semence OGM, plus particulièrement le maïs *Bt.* Pour ce faire, nous avons recours à un modèle entomologique calibré dans lequel la sensibilité du pool génétique des insectes représente une ressource renouvelable. La fonction d'objectif tient compte de la valeur présente des coûts liés à la perte de récolte due aux insectes, ainsi que du surcoût de maïs *Bt.* En absence d'une zone de refuge, le bio-système va converger vers un état stationnaire dans lequel la population d'insectes est complètement résistante au maïs *Bt.*

Nous considérons en premier lieu une zone de refuge qui est contrainte à être constante à travers le temps. Pour les paramètres calibrés du modèle, il s'avère dans ce cas qu'une zone de refuge relativement faible est socialement optimale et que la population d'insectes devient complètement résistante au maïs *Bt.* Dans le cadre d'une analyse de sensibilité portant sur la valeur sélective des gènes résistants à l'OGM, le coût à l'achat de l'OGM ainsi que le taux d'actualisation social, nous trouvons que la convergence vers un état stationnaire dans lequel la population devient complètement résistante représente un résultat général. Uniquement pour un taux d'actualisation social égal à zéro ou un coût à l'achat de l'OGM particulièrement élevé, la zone de refuge est suffisamment élevée pour permettre de garder la sensibilité par rapport à l'OGM du pool génétique à un niveau renouvelable.

En deuxième lieu, nous supposons que la zone de refuge peut varier dans le temps. Comme la fonction d'objectif est linéaire dans la variable de contrôle, le contrôle optimal peut faire intervenir des contrôles extrêmes et singulier. Pour les paramètres calibrés du modèle, nous montrons que la zone de refuge est initialement égale à zéro, puis saute à un niveau strictement entre 0% et 100% à partir duquel elle converge vers le niveau qui permet de maintenir la sensibilité du pool génétique

à un niveau soutenable. Ceci représente un résultat général pour des variations raisonnables des paramètres bio-économiques. Pour le modèle calibré, nous sommes en mesure d'estimer la réduction de coût que procure l'utilisation d'une zone de refuge variable plutôt qu'une zone de refuge invariable.

CHAPITRE 1

ECONOMIC DYNAMICS OF ANTIBIOTIC EFFICACY UNDER OPEN ACCESS

1.1 Introduction

It is a well established fact that antibiotic consumption tends to deplete the efficacy of many antibiotics in combating bacterial infections, as the bacteria develop resistance to the antibiotic.[1] The resulting reduction in the efficacy of antibiotic treatment of many diseases is a matter of growing concern, since it has serious consequences for public health and is the source of important economic costs to society.[2] The problem is complicated by the fact that individual decision makers, acting in their own best interest, do not take into account the effect of their current decisions on the future efficacy of the antibiotic. To realize the social optimum in such a context would require cooperative decision making. Thus the market outcome is unlikely to be socially optimal.

A useful way to approach this problem from an economic perspective is to think of the efficacy of the antibiotic as a common pool resource, much like fisheries for instance. That is the approach we take in this paper. More precisely, we analyze the exploitation of antibiotic efficacy in a market subject to open access on the part of the antibiotic producers to the common pool of efficacy and compare it to the social optimum.

An early contribution to the analysis of the market outcome in a context where the efficacy of a drug is declining in its use can be found in Tisdell (1982). In a highly stylized two-period model, he finds that the market outcome under perfect

[1] For a general overview of the problem of antibiotic resistance see Levy (2002). See also Levy and Marshall (2004) for a recent review of the biological and epidemiological literature on the subject.

[2] See for instance Holmberg, Solomon and Blake (1987), Phelps (1989), US Congress, Office of Technology Assessment (1995), Elbasha (2003) and Laxminarayan (2003).

competition leads to lower efficacy of the drug than would be socially optimal. Our model differs considerably from that of Tisdell in a number of ways. First, we explicitly derive the demand function for the antibiotic under the assumption that individuals differ with respect to their valuation of being in good health. Second, we treat antibiotic efficacy as a common pool renewable resource. Third, we explicitly take into account the dynamic interaction between the level of efficacy of the antibiotic and the level of infection in the population. The underlying dynamic system that describes the evolution of the two state variables, namely the level of antibiotic efficacy and the stock of infected population, is based on an epidemiological model (the SIS-model) borrowed from the biology literature. Fourth, the determination of the social optimum takes into account not only the surplus accruing to the consumers of the antibiotic, but also that of the infected individuals who choose not to buy it and that of the individuals in good health, in addition to the surplus derived by the producers of the antibiotic.

The antibiotic producers care only about the current stock of the infected population, which determines market size, and the current level of antibiotic efficacy, which affects the willingness to pay of the sick population. They ignore the dynamic effects of their decisions. We find that in the open-access equilibrium, the level of antibiotic efficacy tends to a positive steady-state level in which the efficacy renews itself so as to maintain the steady state. It turns out, interestingly, that this steady-state level of antibiotic efficacy can be lower or higher than the level which should prevail in the socially optimal steady state. This will depend on the set of parameters of the model, such as the cost of production and the improvement in the recovery rate that results from treatment, but also the natural recovery rates when infected with a resistant or a susceptible bacterial strain, the rate of transmission of the disease and the discount rate. The paths to steady state will also be different under open access and the social optimum and will involve different treatment rates.

Our approach owes a lot to the papers of Laxminarayan and Brown (2001),

Wilen and Msangi (2003) and Rowthorn and Brown (2003).[3] We make use of the same epidemiological model to describe the dynamics of the antibiotic efficacy and of the infected population and their interaction. However they do not model demand and do not study the market outcome, but concentrate their analysis on the determination of the socially optimal treatment rates. Their objective function is also less general, since it does not take into account the welfare of all the population, whether ill or not and whether being treated or not, as we do here.

The rest of our paper is structured as follows. In section 1.2, we present the epidemiological model that serves as the basis for the biological dynamics that underlie both the open-access equilibrium and the social optimum. In section 1.3, we derive the demand function for the antibiotic. We characterize the open-access equilibrium in section 1.4 and the social optimum in section 1.5. In section 1.6, we compare the open-access outcome to the social optimum. We conclude in section 1.7.

1.2 The epidemiological constraints

In this section we present the basic SIS epidemiological model that describes the population dynamics underlying both the open-access equilibrium and the social optimum. This model assumes that the total population at time t, $N(t)$, can be compartmentalized into the population that is in good health but susceptible to the infection, $S(t)$, and that which is infected, $I(t)$. The infected population is further partitioned into those individuals infected with a drug-susceptible strain, $I_w(t)$, and those infected with a drug-resistant strain, $I_r(t)$. Hence, at any time t, $N(t) = S(t) + I(t) = S(t) + I_w(t) + I_r(t)$.[4]

[3]We should mention also the early contribution of Brown and Layton (1996), who model antibiotic resistance as a dynamic externality. More recently, Gersovitz and Hammer (2004) build on an epidemiological model that is related to the one used here (a form of the so-called SIR-model) to study the economic control of infectious diseases.

[4]The SIS-model is used to describe the dynamics of the population in the case of diseases where once an infected individual recovers he becomes susceptible again, as opposed to diseases where once an individual recovers he becomes immune (the SIR-model). These types of models were first developed by Ross (1911) and Kermack and McKendrick (1927) to study the spread of

Some of the uninfected hosts will become infected through contact with the infected population. The SIS-model assumes that the rate of addition to the infected population in this way is given by $\beta S(t)I(t)$, where β denotes the rate of transmission of the infection between the healthy and the infected population. Some of the infected will recover. In the absence of treatment the natural rates of recovery are r_r for those infected with the drug-resistant strain and r_w for those infected with the drug-susceptible strain. If all the infected are treated with the antibiotic, the rate of recovery of those infected with the drug-resistant strain remains unchanged, while the rate of recovery of those infected with the drug-susceptible strain increases to $r_w + r_f$. If a fraction $f \in [0, 1]$ of the infected population is being treated with the antibiotic, the rate of recovery of those infected with the drug-susceptible strain will be $r_w + fr_f$. Hence the total infected population decreases at the rate $r_r I_r(t) + (r_w + fr_f)I_w(t)$.[5]

Then, if $E(t)$ is the new entries into the population (the births) and if the death rates of the healthy and the infected are respectively n and m, the population dynamics can be described by:

$$\dot{S} = E - nS - \beta S(I_w + I_r) + r_w I_w + r_r I_r + f I_w r_f \tag{1.1}$$

$$\dot{I_w} = (\beta S - m - r_w - fr_f)I_w \tag{1.2}$$

$$\dot{I_r} = (\beta S - m - r_r)I_r. \tag{1.3}$$

We will henceforth assume $E = n = m = 0$, thus taking the total population to be constant. With a constant population, $\dot{S} = -\dot{I}$ and equation (1.1) becomes redundant, being simply the sum of equations (1.2) and (1.3). Furthermore, we can use the fact that $I_r = I - I_w$ to eliminate I_r, leaving two differential equations

diseases in populations. We closely follow the formulation of the SIS-model used by Bonhoeffer, Lipsitch and Levin (1997) and by Wilen and Msangi (2003).

[5]This type of models implicitly assumes that it is not possible to control whether the patient is infected with the resistant or with the susceptible bacteria. This is not an unrealistic assumption when the cost of controlling for the type of bacteria before deciding on the treatment is very high and/or the delays it imposes are long. This seems to be very often the case in practice.

in I and I_w. Now define $w(t) = I_w(t)/I(t)$ as a measure of the efficacy of the antibiotic, as in Laxminarayan and Brown (2001) and Wilen and Msangi (2003). The population dynamics can then be rewritten in terms of the two state variables w and I_w to give:

$$\dot{w} = w(1-w)(\Delta r - r_f f) \tag{1.4}$$

$$\dot{I} = (\beta(N-I) - r_r)I + wI(\Delta r - r_f f) \tag{1.5}$$

where $\Delta r \equiv r_r - r_w$ measures what is called in the epidemiological literature the fitness cost of resistance. The expression "fitness cost" refers here to the fact that although resistance procures the advantage of being able to survive the antibiotic treatment, this advantage comes at a *biological cost* for the resistant strain when $\Delta r > 0$. This is because, with $r_r > r_w$, the resistant strain clears at a faster rate than the susceptible strain in the absence of treatment and hence the susceptible strain naturally ends up dominating the bacteria population in the long-run.

When the fitness cost is zero it can be seen from equation (1.4) that the level of efficacy of the antibiotic can never be replenished, since $f \geq 0$. In that sense the efficacy of the antibiotic can then be considered a nonrenewable resource. On the other hand, if the fitness cost is positive, the level of efficacy can be replenished by setting $f < \Delta r/r_f$ and the efficacy of the antibiotic can be considered a renewable resource. Thus the fitness cost is an important element in the analysis of antibiotic resistance. We will assume the fitness cost to be positive, although it will be fairly straightforward to derive the results for a zero fitness cost as a special case of the more general results.

There exist three steady state configurations to the population dynamics described by (1.4) and (1.5). Let w^{SS} and I^{SS} denote the steady-state values of w and I respectively.

For any $f \neq \Delta r/r_f$, we have $\dot{w} = 0$ for $w = 0$ or $w = 1$ and there are two

distinct steady states, given by:

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_r}{\beta}, 0\right) \tag{1.6}$$

and

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_w - r_f f}{\beta}, 1\right). \tag{1.7}$$

For $f = \Delta r / r_f$, we have $\dot{w} = 0$ for any value of w and hence all

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_r}{\beta}, w \in [0, 1]\right) \tag{1.8}$$

constitute steady states. We will assume throughout $\beta N - r_r > 0$ and $\beta N - r_w - r_f > 0$, thus guaranteing the existence of positively valued steady states for I.

Clearly, the dynamic system described by (1.4) and (1.5) depends in an important way on the proportion f of the population being treated. In particular, if an optimal policy happened to require f to vary over time, then the differential equation system would be non stationary.

Before introducing economic and policy considerations, it is useful to characterize in more detail in (I, w)-space the dynamic behavior of the system for all possible values of f. From (1.5) we verify that

$$\left.\frac{dw}{dI}\right|_{\dot{I}=0} = \frac{\beta}{\Delta r - r_f f}, \tag{1.9}$$

which is the slope of the isocline for I in (I, w)-space. This isocline must go through the point $(I, w) = ((\beta N - r_r)/\beta, 0)$. It is easily verified from equation (1.5) that I is increasing anywhere to the left of the isocline and it is decreasing anywhere to the right.

Consider first the case of $f \in [0, \Delta r / r_f)$. In that case the isocline for I is a positively sloped straight line through $(I, w) = ((\beta N - r_r)/\beta, 0)$ and w is increasing for any $w \in (0, 1)$, as can be seen from equation (1.4). This is illustrated in Figure 1.1, where the arrows indicate the direction of the forces driving (I, w) over time. From

any initial state the system converges to the steady state $((\beta N - r_w - r_f f)/\beta, 1)$. Thus, with a relatively low and constant treatment rate the drug-susceptible bacteria will dominate the bacterial population and the efficacy of the antibiotic will be fully replenished in the long-run. This case includes the case where there is absence of treatment ($f = 0$) and can serve to illustrate the concept of fitness cost. Indeed, it is now immediate that if $f = 0$, then $\Delta r = r_r - r_w > 0$ implies that the susceptible strain will dominate in the long-run.

Figure 1.2 illustrates the position of the $\dot{I} = 0$ isocline for two different values of $f < \Delta r/r_f$. As f is increased from f_1 to $f_2 > f_1$, the $\dot{I} = 0$ isocline pivots to the left through the point $(I, w) = ((\beta N - r_r)/\beta, 0)$. As a consequence the long-run equilibrium will feature a lower steady-state level of infection when a higher (constant) fraction of the infected population is treated.

Consider now the case of $f \in (\Delta r/r_f, 1]$, which is illustrated in Figure 1.3. In this case the isocline for $\dot{I} = 0$ is a negatively sloped straight line through $(I, w) = ((\beta N - r_r)/\beta, 0)$ and w is decreasing for any $w \in (0, 1)$, as indicated by the direction of the arrows in Figure 1.3. Therefore from any initial state the system converges to the steady state $((\beta N - r_r)/\beta, 0)$ and the resistant strain ends up dominating the bacterial population in the long-run.[6]

There remains the case of $f = \Delta r/r_f$. In that case, the $\dot{I} = 0$ isocline is the vertical line going through $(I, w) = ((\beta N - r_r)/\beta, 0)$, as illustrated in Figure 1.4. Any point on this vertical line is then a steady state, since the rate of treatment exactly compensates the fitness cost effect so as to keep the efficacy of the antibiotic stationary, no matter what its level. Hence if the treatment rate is fixed at $\Delta r/r_f$, the system will move horizontally to a stationary point on the I isocline which will depend strictly on the initial level of efficacy of the antibiotic.

Thus far our analysis has been purely descriptive, in the sense that we have limited our attention to the purely biological aspects of the population dynamics,

[6]As in the case of $f \in [0, \Delta r/r_f)$, the $\dot{I} = 0$ isocline will pivot to the left through the point $(I, w) = ((\beta N - r_r)/\beta, 0)$ if f is increased. In this case however the long-run steady state is independent of f since only the resistant strain remains in equilibrium and the level of efficacy of the antibiotic is driven to zero.

without considering how the treatment rate is determined. We now turn to the introduction of economic factors, beginning with the demand for antibiotics, which will allow us to characterize both the open-access equilibrium and the socially optimum uses of the antibiotic, subject to the biological constraints just described.

1.3 The demand for antibiotics

Let θ represent an individual's valuation of being in good health, with θ being distributed over the total population N with distribution function $F(\theta)$. When infected, this individual can choose whether or not to buy the antibiotic at price p.[7] It is assumed that the individual knows whether he is infected or not but, when infected, cannot tell whether he is infected with the drug-resistant or the drug-susceptible strain of the bacteria.

When an individual is infected, the probability of being infected with a drug-resistant strain is given by $\frac{I_r}{I} = 1 - w$, in which case the recovery rate is r_r whether he takes the antibiotic or not. On the other hand, there is a probability $\frac{I_w}{I} = w$ of being infected with the drug-susceptible strain, in which case he can expect to recover at the rate r_w. Therefore the expected recovery rate without treatment is:

$$\pi(w) = wr_w + (1 - w)r_r.$$

If the infected individual buys the antibiotic, he increases his chances of recovery only if the bacterial strain he is suffering from is susceptible to treatment. His expected recovery rate is then increased only by $r_f w$ when he buys the antibiotic, since there is a $1 - w$ chance that the bacteria is resistant. The utility derived from

[7] Our approach to the derivation of demand begs the important question of the doctor-patient relationship, which is beyond the scope of this paper. Actually, it is the doctor who prescribes the antibiotic to the patient. The patient then decides whether to purchase the antibiotic or not. So the demand function for the antibiotic should probably take into account the doctor's decision rule as to whether or not to prescribe the antibiotic as well as the patient's decision process. Introducing the doctor's decision rule would make it possible to address the issue of the doctor's awareness of the dynamic effects of antibiotic consumption on the efficacy of antibiotic and its social welfare implications.

health considerations by the individual of type θ will therefore be given by:

$$u(\theta) = \begin{cases} \theta & \text{if in good health} \\ \pi(w)\theta & \text{if infected and not taking the antibiotic} \\ \pi(w) + r_f w]\theta & \text{if infected and taking the antibiotic.} \end{cases}$$

Denote by $\tilde{\theta}$ the individual type who is indifferent between buying the antibiotic or not when infected. The value of $\tilde{\theta}$ is determined by:

$$\pi(w)\tilde{\theta} = [\pi(w) + r_f w]\tilde{\theta} - p$$

which means that

$$\tilde{\theta} = \frac{p}{r_f w}. \tag{1.10}$$

Individuals with $\theta \geq \tilde{\theta}$ will thus buy the antibiotic and those with $\theta < \tilde{\theta}$ will not. If the whole population N were infected, the proportion of individuals willing to buy the antibiotic would be $[1 - F(\tilde{\theta})]$. But this is not the case: uninfected individuals will not buy the antibiotic. We will assume that the infection spreads equally over the population N, so that being infected and having a certain valuation θ are independent events. Then the fraction of the infected population willing to buy the antibiotic is given by $\frac{I}{N}\left[1 - F\left(\tilde{\theta}\right)\right]$ and, since individuals have a unitary demand, total demand will be:[8]

$$\begin{aligned} Q &= N\frac{I}{N}\left[1 - F\left(\tilde{\theta}\right)\right] \\ &= I\left[1 - F\left(\frac{p}{r_f w}\right)\right]. \end{aligned}$$

[8]Define the joint probability of an individual i being infected and having a valuation of good health higher than $\tilde{\theta}$ as $\Pr(i = \text{infected}, \theta_i \geq \tilde{\theta})$. Then, by independence, we have $\Pr(i = \text{infected}, \theta_i \geq \tilde{\theta}) = \Pr(i = \text{infected}) \Pr(\theta_i \geq \tilde{\theta}) = \frac{I}{N}\left[1 - F\left(\frac{p}{r_f w}\right)\right]$.

Therefore the inverse demand function is:

$$P\left(\frac{Q}{I}, w\right) = r_f w F^{-1}\left(1 - \frac{Q}{I}\right). \tag{1.11}$$

For simplicity, let us assume that θ is distributed uniformly over the population, with supports $[0, 1]$. The inverse demand function then becomes:

$$P\left(\frac{Q}{I}, w\right) = r_f w \left(1 - \frac{Q}{I}\right). \tag{1.12}$$

Notice that the intercept of the inverse demand function is $r_f w$ and its slope is $r_f w/I$. The variable w can be viewed as an (endogenous) index of the quality of the drug, which can vary between zero and one. For $w = 0$, demand is identically zero. For a given size of the infected population, I, the inverse demand curve pivots upwards through the point $(Q, p) = (I, 0)$ as the quality of the antibiotic increases from zero to one and demand is at its highest when $w = 1$.

Because of unitary demand, Q/I represents the fraction of the infected population treated and is thus equal to the parameter f in the dynamic constraints (1.4) and (1.5). The inverse demand function can therefore be rewritten as a function of the fraction of the infected population being treated and the efficacy of the antibiotic to give:

$$P(f, w) = r_f w (1 - f). \tag{1.13}$$

1.4 The open-access equilibrium

In a regime where there is open access to the stock of antibiotic efficacy, antibiotic producers will enter until, at equilibrium, price equals average production costs, thus dissipating any rent that might be had on the common pool of antibiotic efficacy. We will assume that the antibiotic producers are identical, each having a constant unit cost of production of $c > 0$. If $Q(t)$ is the total industry production and sales of the antibiotic under open access, then the open-access equilibrium is

characterized by:

$$P\left(\frac{Q(t)}{I}, w\right) = c. \tag{1.14}$$

Substituting for the inverse demand function (1.12) derived above and assuming $w \neq 0$, we find that:

$$Q(t) = I(t)\left(1 - \frac{c}{r_f w(t)}\right), \tag{1.15}$$

or:

$$f(t) = \frac{Q(t)}{I(t)} = 1 - \frac{c}{r_f w(t)}. \tag{1.16}$$

Hence, under open access, antibiotic production is economically viable and the fraction of the infected population treated will be positive at any date t if and only if $r_f w(t) > c$. Note that since $w(t) \leq 1$, this requires $r_f > c$.

We can now first characterize the different steady states under open-access equilibrium, before turning to the analysis of the transition to a steady state from different possible initial conditions.

1.4.1 The steady states under open access

Consider first the epidemiological steady state given by (1.6). Since the efficacy of the treatment is driven down to zero in this steady state ($w = 0$), so is demand. Any positive production would lead to losses, so that the equilibrium output of the antibiotic will be zero ($Q^{SS} = 0$) and nobody gets treated. This steady state would therefore be characterized in open access by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(0, \frac{\beta N - r_\tau}{\beta}, 0\right). \tag{1.17}$$

However, from (1.13) we know that with $w = 0$, $P(f, w) = 0$. Therefore, since $c > 0$, the equilibrium condition (1.14) cannot hold and such a steady state is ruled out in open access.

In the epidemiological steady state given by (1.7), the quality of the drug is maximal ($w = 1$). Therefore, from (1.16), $f = 1 - c/r_f$ and this steady state will

be characterized in open access by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(1 - \frac{c}{r_f}, \frac{\beta N - r_w - r_f + c}{\beta}, 1\right). \tag{1.18}$$

The steady-state antibiotic production will in this case be

$$Q^{SS} = \left(1 - \frac{c}{r_f}\right)\left(\frac{\beta N - r_w - r_f + c}{\beta}\right).$$

Finally, steady states which satisfy (1.8) occur only when $f = \Delta r/r_f$ and are compatible with any value of $w \in [0, 1]$ in the epidemiological model. But, from (1.16), we see that $f = \Delta r/r_f$ can be the open-access equilibrium treatment rate only if

$$\frac{\Delta r}{r_f} = 1 - \frac{c}{r_f w(t)}. \tag{1.19}$$

This means that w must take on the unique value that satisfies (1.19) in order for the system to be in such a steady state under open access. Hence there is a unique steady state of this type in open access, given by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(\frac{\Delta r}{r_f}, \frac{\beta N - r_r}{\beta}, \frac{c}{r_f - \Delta r}\right). \tag{1.20}$$

In this steady state the aggregate antibiotic production will be

$$Q^{SS} = \frac{\beta N - r_r}{\beta}\left(1 - \frac{r_f - \Delta r}{r_f}\right).$$

Notice that the steady-state configurations (1.18) and (1.20) are mutually exclusive. Which one is relevant will depend on the values of the parameters. To be more precise, if $c = r_f - \Delta r$, they are indistinguishable and $w^{SS} = 1$. If $c < r_f - \Delta r$, then (1.20) must be the relevant steady-state configuration, since this is incompatible with (1.16) when evaluated at $w^{SS} = 1$. If $c > r_f - \Delta r$ then (1.18) must be the relevant steady-state configuration, since it must then be the case that $w^{SS} = 1$ and $f^{SS} = 1 - c/r_f < \Delta r/r_f$.

Notice also that if $c = r_f - \Delta r$ then $c < r_f$ and therefore $f^{SS} > 0$. Furthermore,

if $c \geq r_f$, then $c > r_f - \Delta r$, which means that $w^{SS} = 1$ and hence $f^{SS} = 0$.

1.4.2 The transition to steady state under open access

At time $t = 0$, a stock of infected population $I(0) = I_0 \in (0, N]$ and a stock of efficacy $w(0) = w_0 \in (0, 1)$ are inherited. The initial state is therefore interior, except for possibly $I = N$.[9] As long as $w > c/r_f$, the antibiotic production is economically viable and the firms will enter and produce a positive amount of the antibiotic.

Consider first the case where $c \leq r_f - \Delta r$. From the initial state (I_0, w_0) the open-access equilibrium will then converge asymptotically to the steady state defined in (1.20). To see this, distinguish between four types of states, according as to whether I lies in (I, w)-space to the left or to the right of the $\dot{I} = 0$ isocline and w is greater or smaller than w^{SS}. Let I and II denote states for which $w > w^{SS}$ and III and IV denote states for which $w < w^{SS}$, with states of type I and III lying to the left of the $\dot{I} = 0$ isocline and those of type II and IV to its right. We know from the open-access equilibrium condition (1.16) that $f = 1 - c/r_f w$ and that in the steady state given by (1.20), $w^{SS} = c/(r_f - \Delta r)$. Therefore $w \gtreqless w^{SS}$ is equivalent to $f \gtreqless \Delta r/r_f$ in equilibrium.

We have seen in Section 1.2 that for states of types I and II the $\dot{I} = 0$ isoclines will be negatively sloped and that w will be decreasing over time. As for the stock of infected population, I, it will be increasing over time when to the left of the isocline and decreasing when to the right. We are therefore in a situation such as the one depicted in Figure 1.3 for a fixed $f > \Delta r/r_f$. However, in open

[9] We explicitly ignore the trivial case of $I_0 = 0$, in which case the population remains healthy forever according to equation (1.5). We thereby implicitly assume that some exogenous event occurs initially which causes a portion of the population to become infected by the bacteria. We also assume that a portion of the initially infected population suffers from the resistant strain and a portion suffers from the susceptible strain, so that $I_w(0)$ and $I_r(0)$ are both strictly positive. It then follows that $w_0 (= I_w(0)/I(0))$ is strictly between zero and one. If we had $w_0 = 0$ (everyone is initially infected with the resistant strain) or $w_0 = 1$ (no one is initially infected with the resistant strain), then w remains constant (see equation (1.4)) and the system would converge to either the steady state defined in (1.17) if $w_0 = 0$ or in (1.18) if $w_0 = 1$.

access, as the equilibrium quality of the antibiotic decreases so will the demand for it and, consequently, the fraction of the infected population treated. But since the $\dot{I} = 0$ isocline is not independent of f, this means that the system is non stationary: the $\dot{I} = 0$ isocline will pivot over time towards the right through the point $((\beta N - r_r)/\beta, 0)$, as can be seen from equation (1.9).

Consider then an initial state (I_0, w_0) with an infected population that is relatively low and an antibiotic efficacy relatively high, so that it belongs to type I. Then the dynamics will be as depicted in Figure 1.5. Over time, w decreases and I increases, while the $\dot{I} = 0$ isocline continuously pivots toward the vertical line through $((\beta N - r_r)/\beta, 0)$. At the time at which the $(I(t), w(t))$-path crosses the isocline corresponding to $f(0) = c/r_f w_0$, say at $t = t_1 > 0$, the isocline corresponding to $f(t_1) = c/r_f w(t_1)$ will be further to the right of the initial isocline, as is illustrated in Figure 1.5. The state therefore remains of type I and the path is still decreasing over time. The state will in this way converge asymptotically to the steady state defined in (1.20), as $f(t)$ converges to $\Delta r/r_f$ and the isocline converges to the vertical line through $((\beta N - r_r)/\beta, 0)$.

The situation is different when the initial state is characterized by sufficiently high values of both the efficacy of the antibiotic and the stock of infected population, so as to be of type II, with, as for type I, $f(t) > \Delta r/r_f$. Then, at first, both I and w will be decreasing as will be f. As for type I the isocline is negatively sloped and it is pivoting towards the right as f falls. But this means that at some time, say $t = t_1$, the $(I(t), w(t))$-path will hit the isocline corresponding to $f(t_1)$. At that date, the system switches to the regime in which the state is of type I and $I(t)$ goes from decreasing to increasing. The state again converges in the same way to the steady state defined in (1.20). Such a case is illustrated in Figure 1.6.

A pattern that is in some way similar will occur if the initial state happens to be of type III, with still a relatively high stock of infected population, but now a relatively low level of efficacy of the antibiotic. This is illustrated in Figure 1.7. In this case, since $f(t) < \Delta r/r_f$, w is increasing (see (1.4)) and the $\dot{I} = 0$ isocline is positively sloped and pivoting towards the left as f increases with w (see (1.9)).

For any state of this type, both I and w will be increasing along the equilibrium path. But since the isocline is pivoting towards the left, this means that the state trajectory must, at say $t = t_1$, hit the isocline corresponding to $f(t_1)$. When this occurs, it must be the case that $I(t_1) > I^{SS}$, since the isocline is positively sloped. At that point, there is a switch to a regime in which the state is of type IV, as the stock of infected population goes from increasing to decreasing, and the isocline continues to pivot towards the vertical line through $((\beta N - r_r)/\beta, 0)$.

For any initial state of type IV, the dynamic forces will be pushing w up and I down and f will be increasing with w. The state converges in this way to the steady state defined in (1.20), as the isocline simultaneously converges to the vertical line through $((\beta N - r_r)/\beta, 0)$. This is the case illustrated in Figure 1.8.

Figure 1.9 summarizes these long-run outcomes for the four types of initial states. In all cases, there is convergence to the same steady state, with $f^{SS} = \Delta r/r_f$, $I^{SS} = (\beta N - r_r)/\beta$ and $w^{SS} = c/(r_f - \Delta r)$. When beginning from initial states of type I and IV, the state converges directly to this steady state. When beginning from initial states of type II or III, there is a form of overshooting, in the sense that the stock of infected population moves beyond its steady-state level before, at some point, reversing its direction to converge to that steady state. For an initial state of type II, I is initially higher than I^{SS}, then falls below it before eventually beginning to increase in order to reach I^{SS} again in the long-run. For a type IV initial state, I is initially lower than its steady-state level, moves beyond it and, at some point, begins to decrease towards it in order reach it in the long-run.

To see why the overshooting occurs when the initial state is characterized by either relatively high antibiotic efficacy and high stock of infected population (type II) or relatively low antibiotic efficacy and low stock of infected population (type III), divide both sides of (1.4) by $1 - w$ and both sides of (1.5) by I, and subtract one from the other to get:

$$\frac{\dot{I}}{I} - \frac{\dot{w}}{1-w} = \beta[I^{SS} - I], \tag{1.21}$$

where $I^{SS} = (\beta N - r_r)/\beta$, the long-run stationary stock of infected population.

We immediately see that if the initial state is of either type I or type IV, both sides of this equation are of the same sign, since I and w are initially moving in opposite directions. This will remain so until the steady-state is reached, at which point we have $\dot{I} = \dot{w} = 0$ and $I = I^{SS}$. There can be no overshooting in those cases.

On the other hand, if the initial states are of either type II or type III, then I and w are initially moving in the same direction, with $\left[\frac{\dot{I}}{I} - \frac{\dot{w}}{1-w}\right]$ being initially negative if of type II and positive if of type III and, in both cases, tending to zero over time as I tends to I^{SS}. The left-hand side will go through zero and change sign when I first reaches I^{SS}, with $\frac{\dot{I}}{I} = \frac{\dot{w}}{1-w}$. At that point, I and w will both still be moving in the same direction. But the isocline is pivoting in the direction opposite to the movement of I. Therefore I will eventually have to change direction, since it must at some point cross the $\dot{I}$ isocline.

Consider for example the case of an initial state of type II. Since the antibiotic is very effective and the stock of infected population is high, demand for the antibiotic is high and a large fraction of the infected population gets treated. As a result, both I and w will be decreasing initially. At some point I will reach I^{SS}, but with still $w > w^{SS}$. At that time, I and w are still decreasing, the state still being of type II since the $\dot{I}$-isocline is negatively sloped.[10] But the isocline is pivoting towards the right as the treatment rate decreases and I will eventually have to hit it, after which point I begins to increase, the state having become of type I. We will from that point on have I increasing and w decreasing, until the steady state is reached. While all this is occurring, the treatment rate has been continuously decreasing (see (1.16)), until it also reaches its steady state value of $f^{SS} = \Delta r/r_f$. The same type of reasoning applies when the initial state is of type III.

Notice that if $c = r_f - \Delta r$, then the initial states are necessarily either of type III or type IV. The dynamics is as described above for initial states of those types, with the particularity that the steady state is characterized by $w^{SS} = 1$. As

[10]This can be seen by setting $\dot{I} = 0$ in (1.5) and remembering that $f > \Delta r/r_f$ when the state is either of type II or type I.

already noted in the previous section, if $c = r_f - \Delta r$ then $c < r_f$ and therefore $f^{SS} > 0$.

If the endogenous quality of the drug was initially lower than the economically viable level, that is if $w < c/r_f$, then no antibiotic is produced and the fraction treated is initially zero. But with $f = 0$, w will be increasing. As for I, it will be increasing if of type III (the case illustrated in Figure 1.9) and decreasing if of type IV. Therefore in both cases the state will eventually reach a point where production becomes profitable and producers enter.

We have so far been considering the case where $c \leq r_f - \Delta r$, so that the steady state is as defined in (1.20). Consider now the case where $c > r_f - \Delta r$. Production cost is then relatively high and, as was the case for $c = r_f - \Delta r$, $f < \Delta r/r_f$, so that initial states are necessarily of either type III or type IV. The corresponding dynamics will be as described above for those types of states, except for the fact that the level of antibiotic efficacy will now attain $w = 1$ before the stock of infected population can reach the level $I = (\beta N - r_r)/\beta$. The relevant steady state configuration is then that given by (1.18), with $w^{SS} = 1$ and $I^{SS} = (\beta N - r_w - r_f + c)/\beta > (\beta N - r_r)/\beta$. Because of the relatively high cost, the treatment rate will be relatively low. In particular, if $c \geq r_f$, which implies $c > r_f - \Delta r$, the open-access steady state will be of this type, but with $f^{SS} = 0$, as well as $f = 0$ all along the path leading to it.

1.5 The social optimum

The instantaneous social welfare is given by the sum of the surplus of all consumers, whether or not they are infected and, when infected, whether or not they buy the antibiotic, and the surplus of the antibiotic producers. It can be written

as:

$$
\begin{aligned}
& W(f,w,I) \\
&= N\int_0^1 u(\theta)d\theta - cfI \\
&= (N-I)\int_0^1 \theta d\theta + I\int_0^{\tilde{\theta}(p)} \pi(w)\theta\ d\theta + I\int_{\tilde{\theta}(p)}^1 \{[\pi(w)+r_f w]\theta - p\}\ d\theta + [p-c]fI \\
&= \frac{1}{2}(N-I) + \frac{1}{2}\pi(w)I + \frac{1}{2}r_f wIf^2 + [r_f w(1-f) - c]fI, \qquad (1.22)
\end{aligned}
$$

where $p = P(f,w) = r_f w(1-f)$ is the price of the antibiotic and, exactly as in (1.10), $\tilde{\theta}(p) = \frac{P(f(t),w)}{r_f w} = (1-f)$ defines the consumer who is indifferent between buying or not buying the antibiotic.

The first of those four terms is the surplus derived by that portion of the population which is in good health, $\theta = 1/2$ being the mean valuation of good health. The second term is the surplus accruing to that portion of the infected population which values good health at less than $\tilde{\theta}(p)$ and hence chooses not to buy the antibiotic. They recover at the natural recovery rate $\pi(w)$. The third term is the surplus that accrues to those who choose to buy the treatment at price p, since they have a valuation of good health higher than $\tilde{\theta}(p)$. They recover at the augmented rate $\pi(w) + r_f w$. The last term is the surplus of the producers of the antibiotic.

Determining the social optimum means choosing the path of $f(t)$ so as to maximize:

$$\int_0^\infty e^{-\rho t} W(f(t), w(t), I(t))dt \qquad (1.23)$$

subject to the differential equations (1.4) and (1.5), which determine the evolution of the state variables $w(t)$ and $I(t)$, and to $0 \leq f \leq 1$. The given initial conditions are $w(0) = w_0$ and $I(0) = I_0$ where, by assumption, $w_0 \in (0,1)$ and $I_0 \in (0,N]$ (see footnote 9).[11]

[11]The state variables are also constrained, since we must have $w(t) \in [0,1]$ and $I(t) \in [0,N]$. We neglect those constraints, since, if $w(t)$ reaches either 1 or 0, it will stay there forever. As

The current value Hamiltonian for this problem is given by:

$$\begin{aligned} H(f,w,I,\mu,\lambda) &= \frac{1}{2}(N-I)+\frac{1}{2}\pi(w)I+r_f wfI-\frac{1}{2}r_f wIf^2-cfI \\ &\quad +\mu w(1-w)(\Delta r-r_f f) \\ &\quad +\lambda I[(\beta(N-I)-r_r+w(\Delta r-r_f f)] \end{aligned} \tag{1.24}$$

and its derivative with respect to the control variable f is:

$$\frac{\partial H}{\partial f}=\left[r_f w(1-f^*)-c\right]I-r_f w\left[\mu(1-w)+\lambda I\right], \tag{1.25}$$

where μ and λ are the shadow values associated to the level of antibiotic efficacy and to the stock of infected population respectively.

The following conditions, as well as (1.4) and (1.5), are necessary for an optimum:

$$\frac{\partial H}{\partial f}\leq 0,\quad \frac{\partial H}{\partial f}f=0,\quad f\geq 0 \qquad \text{or} \qquad \frac{\partial H}{\partial f}\geq 0,\quad \frac{\partial H}{\partial f}(1-f)=0,\quad f\leq 1 \tag{1.26}$$

$$\rho\mu-\dot{\mu} = r_f fI-\frac{1}{2}r_f f^2 I-\frac{1}{2}\Delta rI+(\Delta r-r_f f)[\mu(1-2w)+\lambda I] \tag{1.27}$$

$$\begin{aligned} \rho\lambda-\dot{\lambda} &= r_f wf-\frac{1}{2}r_f wf^2-cf-\frac{1}{2}(1-\pi(w)) \\ &\quad +\lambda[\beta(N-2I)-r_r+w(\Delta r-r_f f)]. \end{aligned} \tag{1.28}$$

Condition (1.26) is the first-order condition for the maximization of the Hamiltonian with respect to $f(t)$ at each t. Conditions (1.27) and (1.28) are the arbitrage equations that determine the evolution of $\mu(t)$ and $\lambda(t)$.

---

for $I(t)$, for any interior value to the left of the $\dot{I}=0$ isocline, the dynamic forces always push it away from 0, and, for any value to the right of the $\dot{I}=0$ isocline, including $I=N$, those forces always push it away from N. See the discussion of the epidemiological dynamics of Section 1.2.

In the case of an interior solution for f, condition (1.26) can be written:

$$r_f w(1-f) = c + \frac{r_f w}{I}\left[\mu(1-w) + \lambda I\right]. \tag{1.29}$$

The left-hand side of this equation is the price of the antibiotic. The condition says that the price of the antibiotic must be equal to the full marginal cost of treatment, which is the sum of the marginal cost of producing the antibiotic, c, and the marginal opportunity cost — through its effect on both the quality of the antibiotic, w, and the stock of infected population, I, — of using it to treat a fraction f of the infected population.

The variable μ measures the marginal shadow price of antibiotic efficacy. The variable $w(= I_w/I)$ being the level of antibiotic efficacy, its complement, $1-w$ $(= I_r/I)$, measures the level of antibiotic resistance. Hence $\mu(1-w)$ evaluates the level of antibiotic resistance at the marginal shadow price μ. The variable λ measures the marginal shadow cost of infection.[12] Hence λI is the implicit (negative) value of the stock of infected population, evaluated at λ. The sum of those two terms, $[\mu(1-w)+\lambda I]$, can be either positive or negative and can possibly change sign over time. When positive (negative), the overall net opportunity cost — in excess of the marginal cost of production c —, of marginally increasing the fraction of the infected population treated is positive (negative). The socially optimal price of the antibiotic at that date will then be higher (lower) than the marginal cost of production.

Contrary to the competitive producers in an open-access regime, the socially optimal solution takes into account the fact that the current treatment decision affects both the future level of efficacy of the antibiotic and the future stock of infected population. This is reflected in the expression $[\mu(1-w)+\lambda I]$ and its sign. In open access the producers act myopically and enter until price is driven to average cost. As shown in Section 1.4, this means that $f = 1 - c/r_f w$ in

[12]Numerical simulations indicate that λ is indeed negative, as expected, whereas μ is positive.

equilibrium.[13] If we now denote by an asterisk the socially optimal values of the variables, then, using (1.29), we can write, for any t:

$$f(t) - f^*(t) = \left(\frac{w(t) - w^*(t)}{r_f w(t) w^*(t)}\right) c + \frac{1}{I^*(t)} \left[\mu^*(t)(1 - w^*(t)) + \lambda^*(t) I^*(t)\right]. \quad (1.30)$$

We see that for identical levels of antibiotic efficacy — for instance at $t = 0$ —, the fraction treated under open access will be greater than is socially optimal if $[\mu(1 - w) > -\lambda I]$, since the full social cost of treatment then exceeds the cost of producing the antibiotic. The reverse is true if $[\mu(1 - w) < -\lambda I]$.

1.5.1 The steady states in the social optimum

Setting $\dot{w} = \dot{I} = \dot{\mu} = \dot{\lambda} = 0$ generates a socially optimal steady state. Consider first the epidemiological steady state given by (1.6). The antibiotic is completely inefficient in this steady state ($w = 0$). Therefore no socially valuable production can take place and the steady state of this type at the social optimum is:

$$(f^{SS^*}, I^{SS^*}, w^{SS^*}) = \left(0, \frac{\beta N - r_r}{\beta}, 0\right). \quad (1.31)$$

This steady state turns out to be unstable so that, when starting from an initial state (I_0, w_0) which is interior, the system will move away from it.[14] We can therefore ignore it in what follows.

In the epidemiological steady state given by (1.7), antibiotic efficacy is at its maximum level ($w = 1$). Setting $w = 1$ in (1.26), in (1.5) with $\dot{I} = 0$ and in (1.28) with $\dot{\lambda} = 0$ yields three equations in I, λ and f whose solution for those three variables will depend strictly on the parameters of the problem. This is shown in

[13] Marginal cost is what matters for the determination of the social optimal price, whereas average cost is what matters in the determination of the open-access equilibrium price. Because of our assumption that the unit cost of production is constant, we have marginal cost equal to average cost.

[14] Linearizing the system of differential equations (1.4), (1.5), (1.27) and (1.28) with f satisfying (1.26), it is verified that the trace of the matrix of the linearized system is positive when evaluated at this steady state.

the Appendix, where it is also shown that any $f \in [0,1]$ can be part of the solution to those equations given appropriate values of the parameters. The socially optimal fraction of the sick population treated at this steady state will therefore depend on the parameters of the model and can take on any value from zero to one. This means that when this is the relevant steady state configuration, we will have:

$$(f^{SS^*}, I^{SS^*}, w^{SS^*}) = \left(f \in [0,1], \frac{\beta N - r_w - r_f f}{\beta}, 1 \right) \tag{1.32}$$

Finally, the relevant description of the steady state can be of the type characterized by (1.8). This steady state is shown in the Appendix to be given by:

$$(f^{SS^*}, I^{SS^*}, w^{SS^*}) = \left(\frac{\Delta r}{r_f}, \frac{\beta N - r_r}{\beta}, -\frac{J}{2H} + \sqrt{\left(\frac{J}{2H}\right)^2 - \frac{K}{H}} \right) \tag{1.33}$$

where

$$\begin{aligned} H &= (r_f - \Delta r)\frac{\Delta r(r_r - \beta N)}{2\rho} \\ J &= (r_f - \Delta r)(\rho + \beta N - r_r)\left(\frac{\Delta r}{2\rho} - 1\right) + \frac{r_f}{2}(r_r - 1) - c\Delta r \\ K &= c(\rho + \beta N - r_r). \end{aligned}$$

The steady state configurations (1.33) and (1.32) are mutually exclusive. In fact, when $w^{SS^*} = 1$ in (1.33) they are indistinguishable. This will occur when (see the Appendix):

$$c = \tilde{c}(r_f) = \frac{\Delta r\left[\frac{\Delta r}{2} - (\beta N - r_r + \rho)\right]}{\beta N - r_r + \rho - \Delta r} + \left(\frac{\beta N - r_r + \rho + \frac{1}{2} - \frac{1}{2}(\Delta r + r_r)}{\beta N - r_r + \rho - \Delta r}\right) r_f. \tag{1.34}$$

For $c \leq \tilde{c}(r_f)$, the socially optimal steady state will be as defined in (1.33). For $c > \tilde{c}(r_f)$, it will be as defined in (1.32).

Notice also that in order to have $w^{SS^*} = 0$ in (1.33), it must be the case that $K = 0$. But this is not possible, since $c > 0$. Therefore the socially optimal level

of antibiotic efficacy will be strictly positive.

As shown in the Appendix, when $w^{SS^*} = 1$, we must have:

$$f \quad \begin{cases} > 0 \quad \text{if} \quad c < \left(1 + \dfrac{1 - r_w}{2(\beta N - r_w + \rho)}\right) r_f \\ \\ = 0 \quad \text{if} \quad c > \left(1 + \dfrac{1 - r_w}{2(\beta N - r_w + \rho)}\right) r_f > r_f. \end{cases} \tag{1.35}$$

1.5.2 The transition to steady state in the social optimum

The social planner takes into account the full marginal cost of treatment, which reflects the shadow values attached to the efficacy of the drug and to the infected population in addition to the unit cost of production. Because of this it is not the case that $w \gtreqless w^{SS^*}$ corresponds to $f \gtreqless \Delta r/r_f$, as it was in the open-access equilibrium. The definitions of the four types of state introduced in Section 1.4.2 are still valid after replacing w^{SS} by w^{SS^*}, but they cannot be expressed in terms of f being greater or smaller than $\Delta r/r_f$ anymore. This means that the direction of movement of w may change as f goes from, say, $f > \Delta r/r_f$ to $f < \Delta r/r_f$ although the state remains of the same type. It therefore becomes much more complicated to fully describe analytically the dynamic forces within each type of state, which themselves depend on the parameters and on the initial state. For this reason, we rely on numerical simulations to explore the transition to steady state.[15] We report here, for illustrative purposes, simulations for a set of parameters such that $c < \tilde{c}(r_f)$, so that the steady state is as defined in (1.33). The simulations show that the system converges to this steady state when beginning from an initial state which satisfies $I \in (0, N]$ and $w \in (0, 1)$. Similar simulations have been carried

[15]For simulations purposes, the continuous time and continuous variables problem was approximated by a discrete time and a discrete variables problem. The numerical simulations were then performed by formulating the optimal control problem in a recursive way. We used the value function iteration procedure (see Judd (1998), pages 412–413) to determine the value function V that satisfies the Bellman equation corresponding to the recursive formulation. The simulations were run with numerous parameter sets in order to verify the robustness of the results. We also verified that the steady-state results obtained numerically for the state, co-state and control variables correspond to those obtained analytically. In particular, we have made sure that the co-state variables μ and λ satisfy $\mu = \partial V/\partial w$ and $\lambda = \partial V/\partial I$ at the steady state.

out for the case of $c > \tilde{c}(r_f)$, with similar results. Recall that in this last case, the states can only be of either type III or type IV.

Figure 1.10 illustrates the evolution of (I, w) beginning from the four possible types of initial states, each with the same properties as in the corresponding Figure 1.9 for the open-access equilibrium:[16] one with the initial state to the left of the $\dot{I} = 0$ isocline (type I) and one to its right (type II), both with $w_0 > w^{SS^*}$; one with the initial state to the left of the isocline (type III) and one to its right (type IV), both with $w_0 < w^{SS}$.[17]

As with the open-access equilibrium, the system tends in the long-run to a steady state in which the treatment rate is such that antibiotic efficacy renews itself in order to maintain its steady state level. The steady-state stock of infected population $((\beta N - r_r)/\beta)$ and the steady-state treatment rate $(\Delta r/r_f)$ will be the same as in the open-access equilibrium. The steady-state quality of the antibiotic will in general be different, although it is conceivable that it be the same as well. But in all cases, the approach to the steady state will differ.

1.6 Comparing the socially optimal and the open-access steady states

Whether the steady-state level of antibiotic efficacy in the social optimum is higher or lower than in the open-access regime depends crucially on the values of the parameters. In what follows we concentrate on the parameters r_f and c, which measure respectively the increase in the recovery rate resulting from treatment and the unit cost of production of the antibiotic.

Equating the steady-state values for w in (1.20) and (1.33), we find that we will

[16]The simulations represented in Figure 1.10 were run with the following parameter values: $\beta = 0.6, r_r = 0.25, r_w = 0.15, r_f = 0.3, N = 1, c = 0.1, \delta = 0.971$, where δ represents the time discrete discount factor.

[17]The case where the initial state is of type III in Figure 1.10 illustrates a situation where $\dot{w}$ goes from negative to positive while the state (I, w) remains of type III. This is because the optimal treatment rate is initially greater that $\Delta r/r_f$ but decreasing. When it reaches $\Delta r/r_f$ it continues to decrease for some time before beginning to increase again to reach $f = \Delta r/r_f$ at the steady state. But as f goes from greater to smaller than $\Delta r/r_f$, w goes from decreasing to increasing and moves over time towards its steady state level w^{SS^*}.

have $w^{SS^*} = w^{SS}$ for:

$$c = -\frac{\Delta r(\beta N - r_r + \rho)}{\beta N - r_r + 2\rho} + \left(\frac{\Delta r(\beta N - r_r + \rho) + \rho(r_r - 1)}{\Delta r(\beta N - r_r + 2\rho)}\right) r_f. \tag{1.36}$$

This is a straight line in (r_f, c) space. Its intercept is negative and the sign of its slope depends on the sign of $\Delta r(\beta N - r_r + \rho) + \rho(r_r - 1)$.[18] For any point above that line, we will have $w^{SS^*} \leq w^{SS}$ (with strict inequality as long as $w^{SS^*} < 1$), while for any point below it we have $w^{SS^*} > w^{SS}$. Thus for any given value of r_f, if the cost of producing the antibiotic is sufficiently large, the open-access equilibrium will result in a higher steady-state level of antibiotic efficacy than is socially optimal. In fact, if the slope of this line is negative, this will always be the case. On the other hand, when the slope is positive, there will exist some values of r_f such that for a low enough cost of production the social optimum will require a higher steady-state level of antibiotic efficacy than what would result in open-access. This is the case represented in Figure 1.11, where condition (1.36) is drawn as a solid line. Notice that the slope will be positive for ρ sufficiently small and it will be positive for any ρ if $\Delta r > 1 - r_r$.

From the analysis of the open-access steady state in section 1.4, we know that for $c \geq r_f - \Delta r$ we will have $w^{SS} = 1$. The condition $c = r_f - \Delta r$ is drawn as a dashed line in Figure 1.11. This line will always lie above the line representing $w^{SS^*} = w^{SS}$ in the positive quadrant. For points on it, the open-access steady-state configurations (1.18) and (1.20) are indistinguishable. For points above it, the open-access steady state is as defined in (1.18), with $w^{SS} = 1$ and $I^{SS} = (\beta N - r_w - r_f + c)/\beta > (\beta N - r_r)/\beta$. The open-access steady state has $f^{SS} > 0$ for points between the line $c = r_f - \Delta r$ and the forty-five degree line $c = r_f$, but $f^{SS} = 0$ for points above the line $c = r_f$.

Also depicted in Figure 1.11 is the straight line defined by $c = \tilde{c}(r_f)$. For points on it $w^{SS^*} = 1$ and the socially optimal steady-state configurations (1.33)

[18] Recall that $\beta N - r_r$ was assumed positive from the outset, in order to guarantee the existence of positive steady states.

and (1.32) are indistinguishable. For points above it, we have $w^{SS^*} = 1$ but with $I^{SS^*} = (\beta N - r_w - r_f f)/\beta > (\beta N - r_r)\beta$ as in the socially optimal steady-state configuration (1.32). As can be seen from (1.35), when $w^{SS^*} = 1$ and

$$r_f < c < \left(1 + \frac{1 - r_w}{2(\beta N - r_w + \rho)}\right) r_f,$$

the socially optimal rate of treatment will be positive, whereas the firms would find it unprofitable to produce the drug in open-access equilibrium and hence the treatment rate would be zero. This steady-state threshold level of social profitability is higher than is the threshold level of private profitability, since the socially optimal solution takes into account the welfare of the whole population and the epidemiological dynamics, contrary to the firms in open access.

For illustrative purposes, Figure 1.12 depicts numerical simulations that compare the transitions to steady state for a case where the initial state (I_0, w_0) is of type II (see Figures 1.9 and 1.10) and the steady-state level of antibiotic efficacy is lower in the social optimum than in open access. The evolution of the state paths have in common the "overshooting" pattern in the level of infection, which is stronger in the social optimum than in open access. This means that although in both cases it will end up at the same steady-state level, for a good part of the socially optimal trajectory the stock of infected population will be maintained below the minimal level reached under open access. The level of antibiotic efficacy decreases in a monotone fashion in each case and it is always higher in open access than what it would be in the social optimum for the same stock of infected population, except for a single point where the two paths cross. This suggests that the socially optimal fraction of the infected population treated at each instant will be greater than under open access, except asymptotically as both tend to the same steady state value of $\Delta r/r_f$. This is indeed verified numerically, as shown in Figure 1.13.

Similar numerical simulations with initial states of types I, III or IV and with w^{SS^*} greater, smaller or equal to w^{SS} yield, *mutate mutandis*, similar qualitative

results.

1.7 Conclusion

We have modeled the level of efficacy of an antibiotic in treating a bacterial infection as a resource stock which is depleted by consumption of the antibiotic, as the bacteria become resistant, but which may be renewed if managed properly. This has served as the basis for analyzing the economic dynamics of the use of the antibiotic to treat a bacterial infection under two scenarios. One is the market equilibrium in which antibiotic producers have open access to the common pool of antibiotic efficacy and enter until price is driven down to average cost. They care only about their production cost and the determinants of current demand for their product, which are its quality, as measured by the current level of efficacy of the antibiotic, and the current stock of infected population, but they ignore their individual effects on the evolution of those state variables. The other is the social optimum, which takes into account, in addition to the surplus of the producers, the welfare of all the population, whether healthy or infected and, when infected, whether treated with the antibiotic or not.

It turns out that the comparison of the steady-state level of antibiotic efficacy under the two scenarios is ambiguous. Consider a parameter configuration such that the steady state level of antibiotic efficacy is less than one in both the open access equilibrium and the social optimum. Then, whether the steady-state level of efficacy in open-access equilibrium is lower or higher than in the socially optimal steady-state will depend on the epidemiological and the economic parameters. For instance, for a given cost of production of the antibiotic, if the increase in the recovery rate that results from treating the infection is sufficiently high, then the socially optimal steady-state level of antibiotic efficacy can be higher than in the open-access equilibrium, but the reverse is true if the increase in the recovery rate is sufficiently low. In both cases, the steady-state stock of infected population and the steady-state treatment rate will be the same in the open-access equilibrium as

in the social optimum. But the trajectories leading to those long-run steady-states will always differ considerably.

There in fact exist some parameter configurations such that the steady state level of efficacy would be equal to one under open access while it would be less than one at the social optimum. This will involve a unit cost of production which is relatively high and hence a relatively low treatment rate under open access. Should the unit cost of production exceed the improvement in the recovery rate that results from treatment, the open access treatment rate would be zero in such an open-access steady state, since the firms would find it unprofitable to produce. The threshold cost level for social profitability of treatment is however higher than this, because, contrary to the firms under open access, the social optimum takes into account the welfare of all the population, whether healthy or not, as well as the epidemiological dynamics.

The open-access equilibrium and the social optimum are two benchmark cases. Pharmaceutical companies are usually given patent rights for the production of the drug they have discovered in order to encourage research and development, with the result that they benefit from a monopoly situation for a finite period of time. The open-access scenario can be viewed as a good approximation of the situation which arises after the expiration of the patent. An obvious next step, which is the subject of ongoing research, is to analyze and compare to the social optimum a situation where a producer has monopoly rights for a finite period of time and becomes one of many producers in open access once those monopoly rights expire. The analyses and comparisons carried out in this paper provide useful inputs for further research in this direction. They should also have useful implications for the analysis of optimal policies towards antibiotic use in general, although, given the complicated dynamics involved and the ambiguities encountered in comparing the two benchmark scenario, one can expect the task to be arduous.

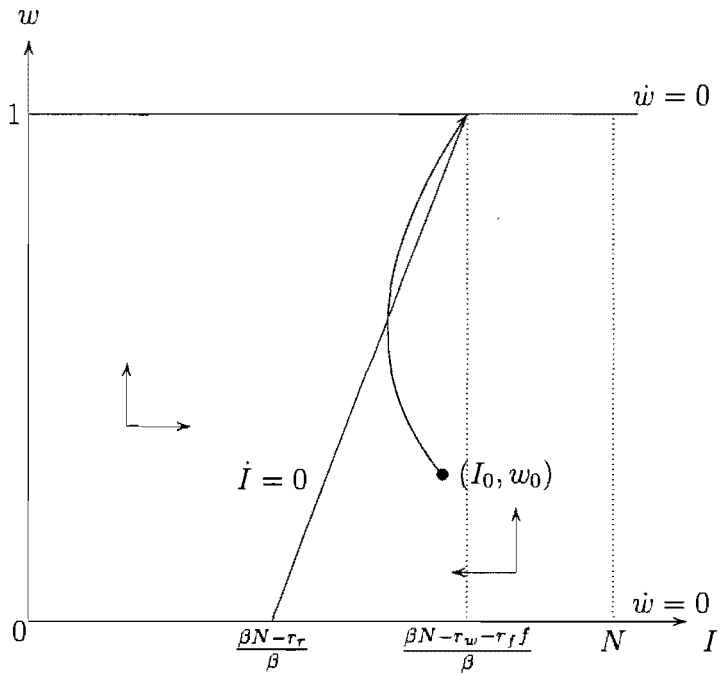

Figure 1.1: Epidemiological dynamics with $f \in \left[0, \frac{\Delta r}{r_f}\right)$

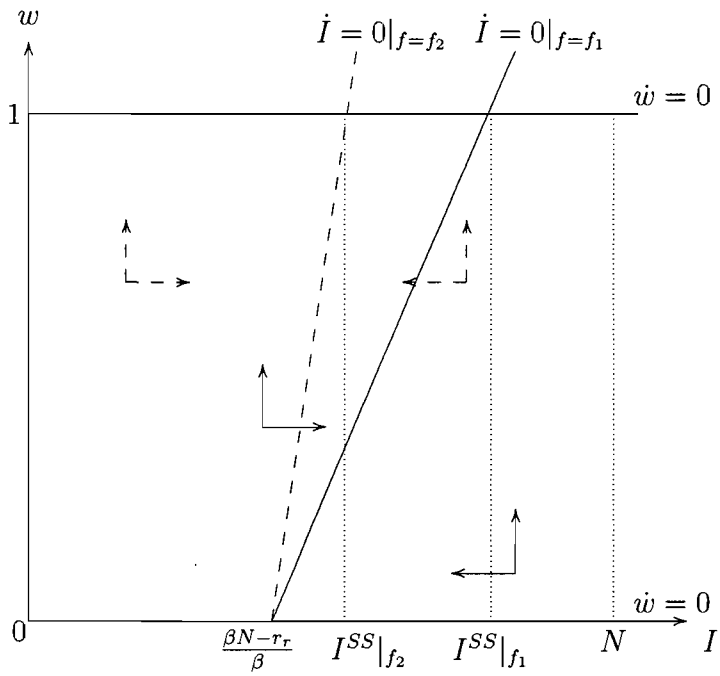

Figure 1.2: Epidemiological dynamics with $f_1 < f_2 < \frac{\Delta r}{r_f}$

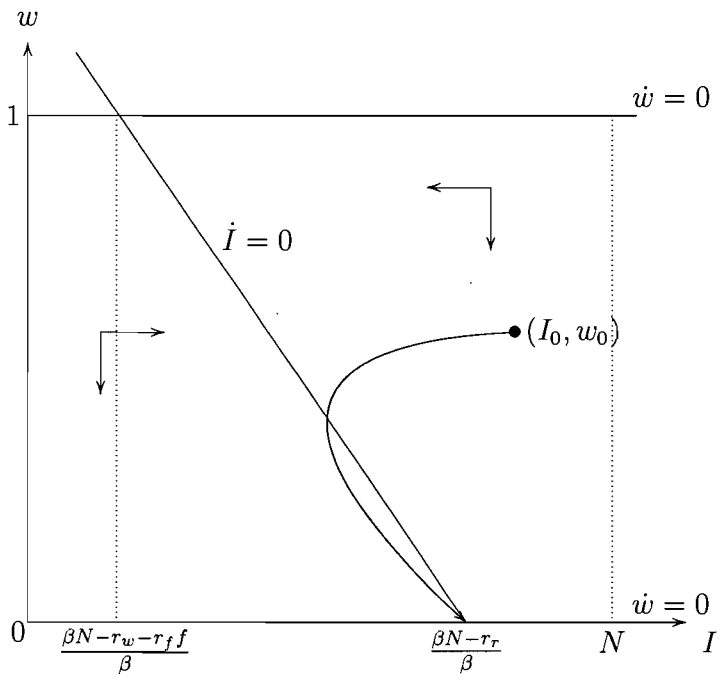

Figure 1.3: Epidemiological dynamics with $f \in \left(\frac{\Delta r}{r_f}, 1\right]$

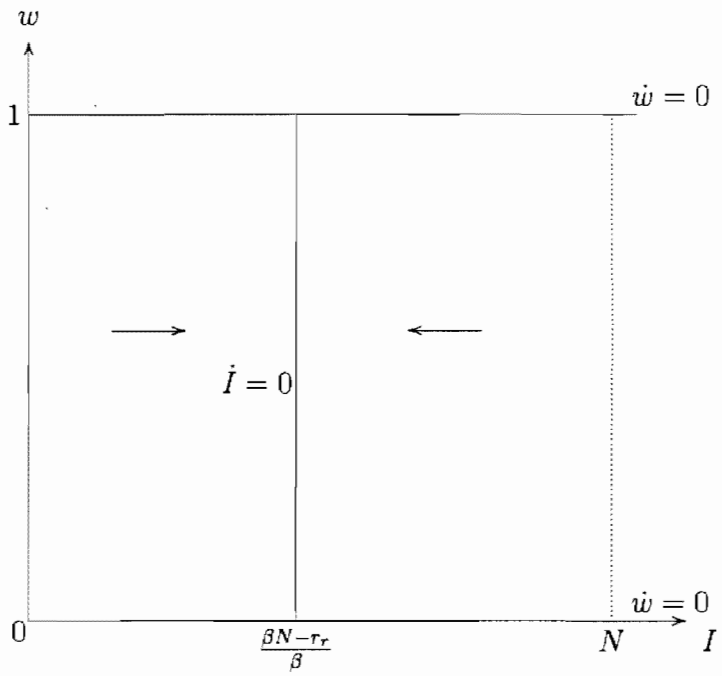

Figure 1.4: Epidemiological dynamics with $f = \frac{\Delta r}{r_f}$

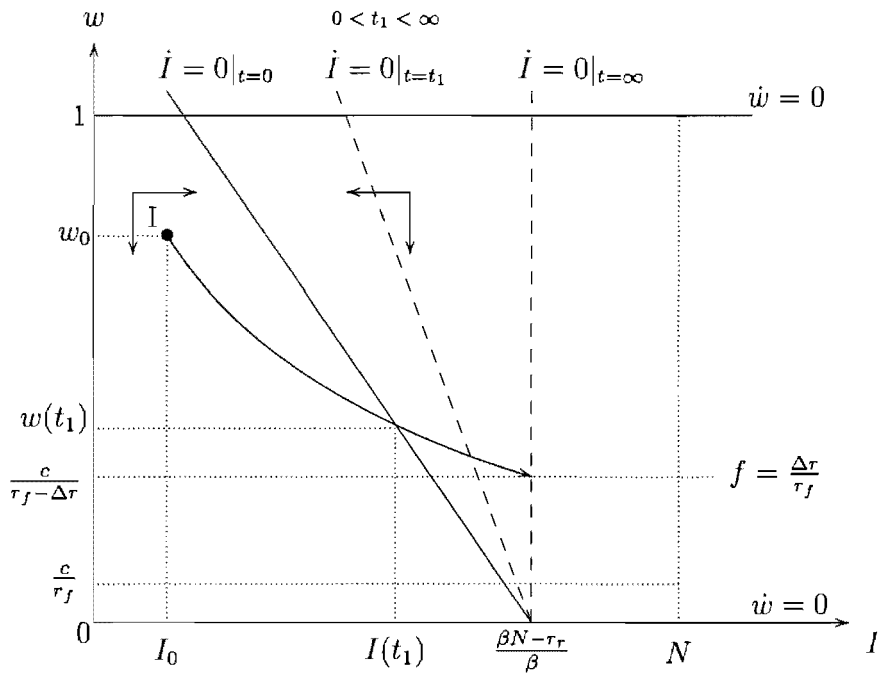

Figure 1.5: Open-access dynamics with initial state of type I

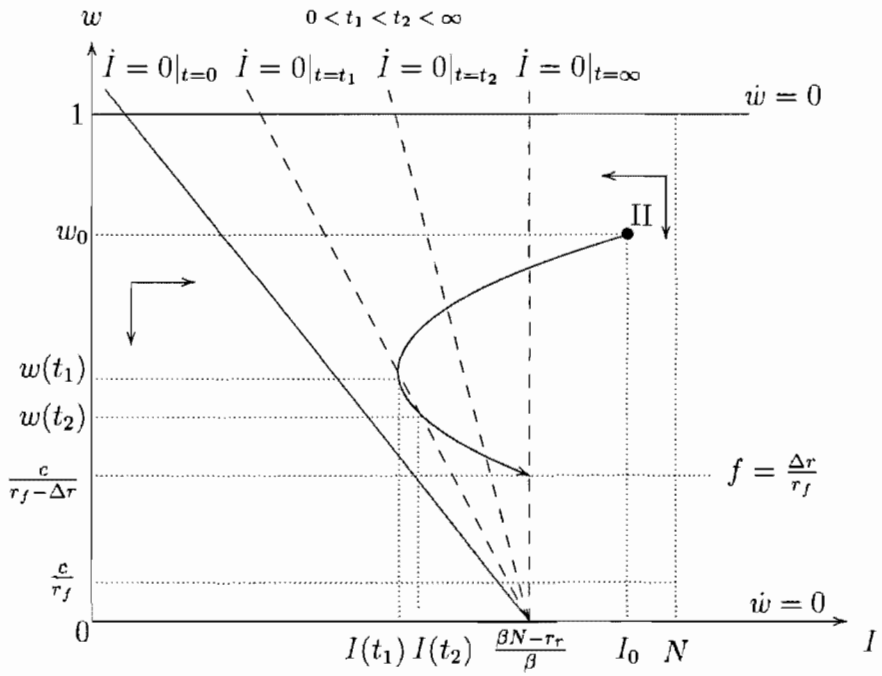

Figure 1.6: Open-access dynamics with initial state of type II

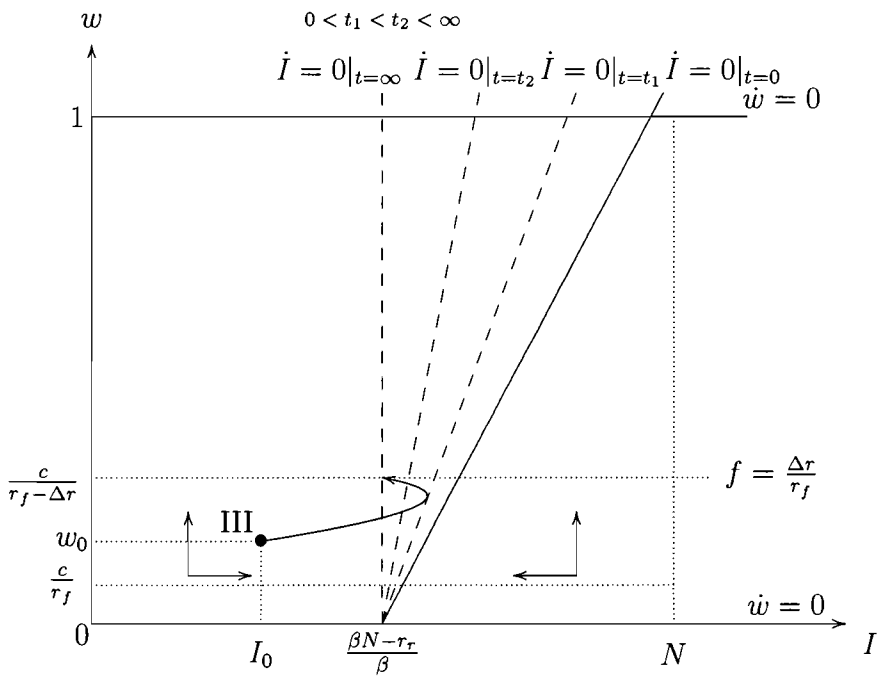

Figure 1.7: Open-access dynamics with initial state of type III

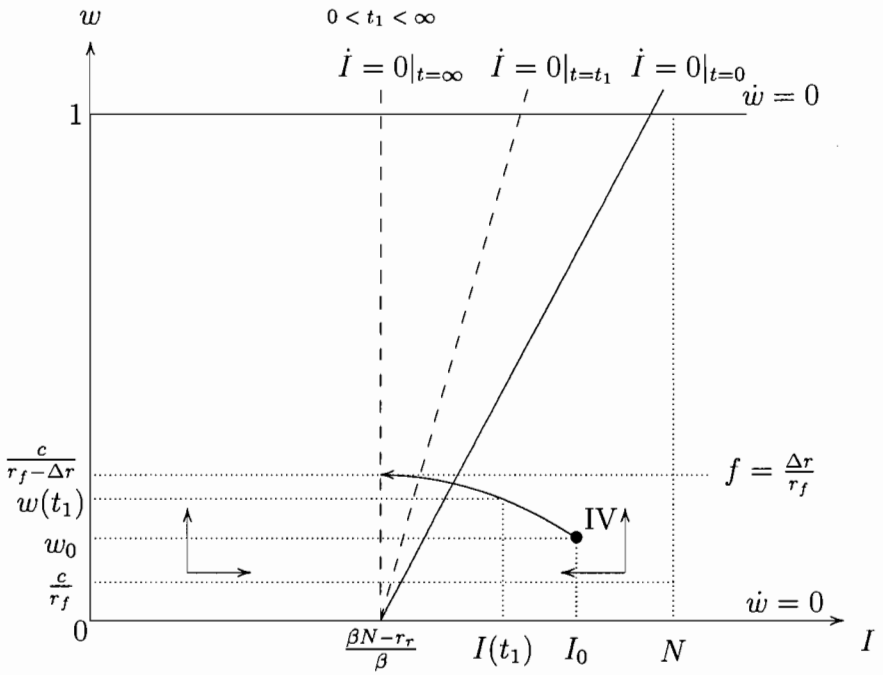

Figure 1.8: Open-access dynamics with initial state of type IV

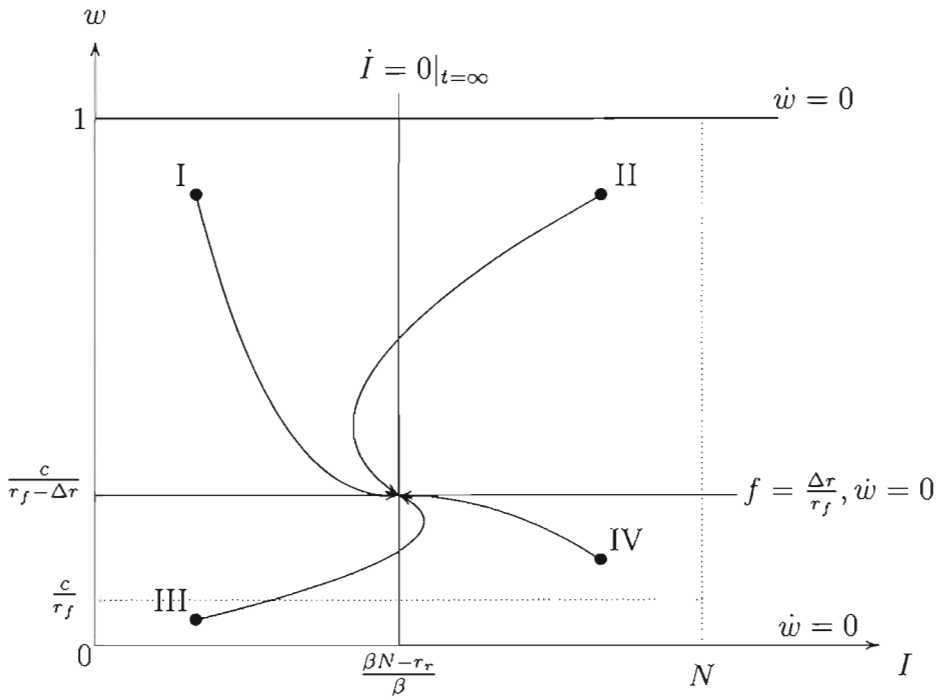

Figure 1.9: Convergence to steady state under open access

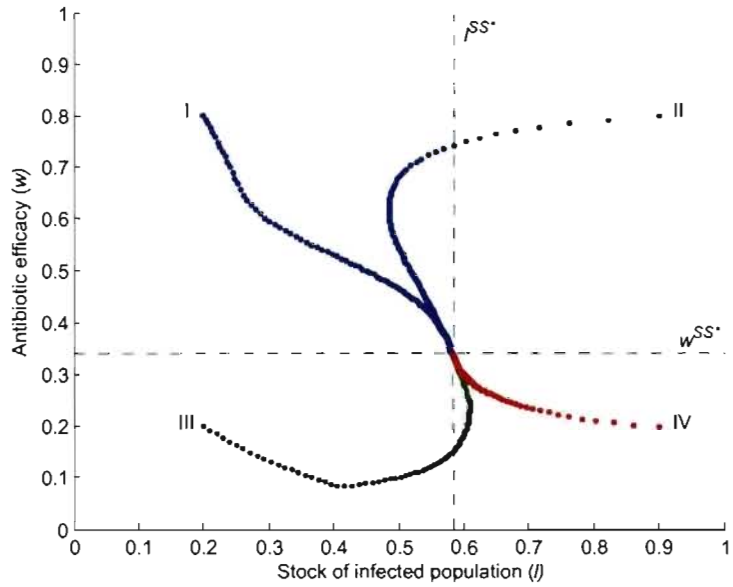

Figure 1.10: Convergence to steady state in the social optimum

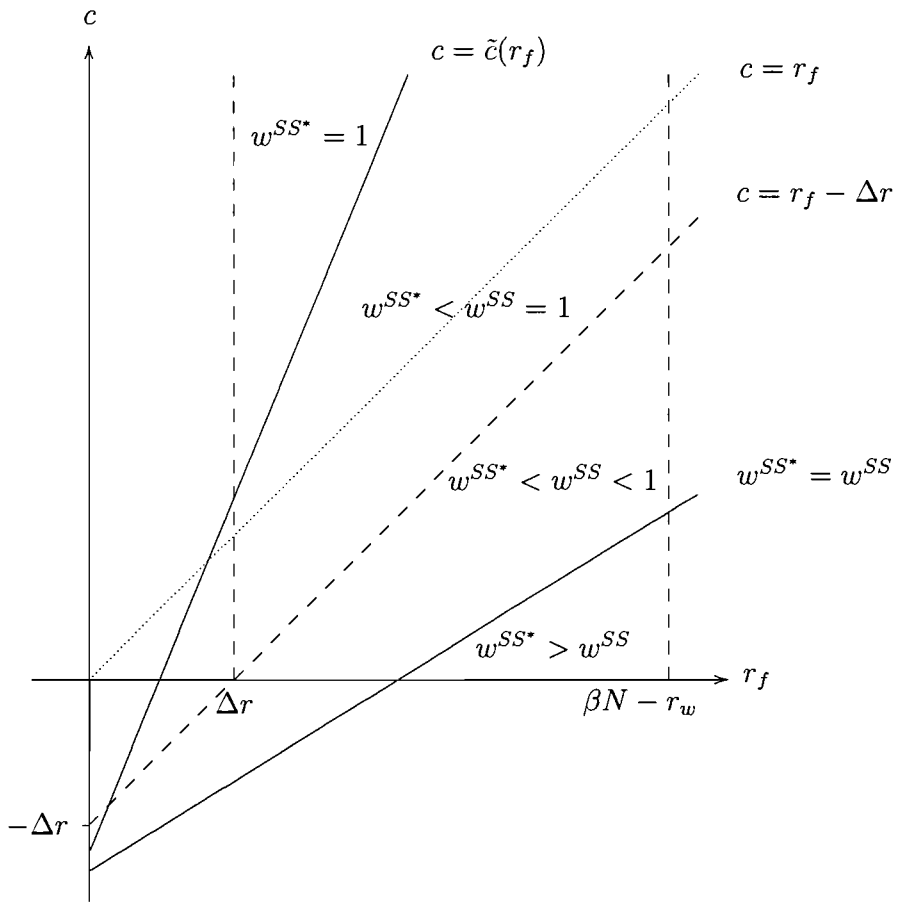

Figure 1.11: Comparison of the steady states

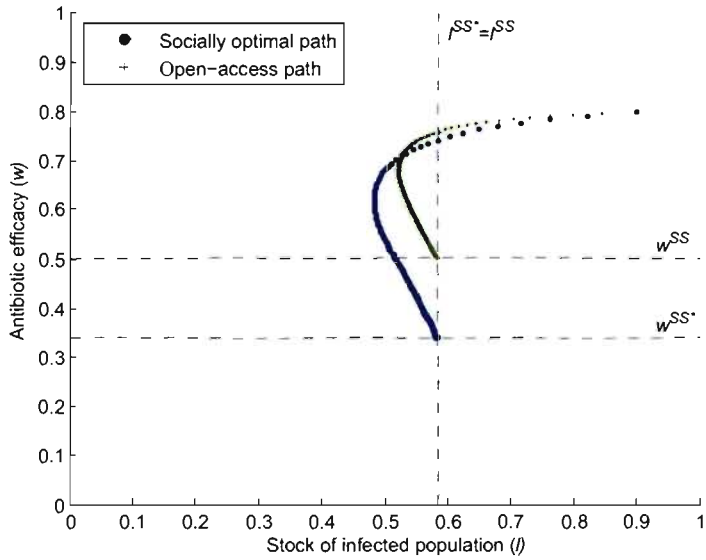

Figure 1.12: Comparison of the socially optimal and open-access paths

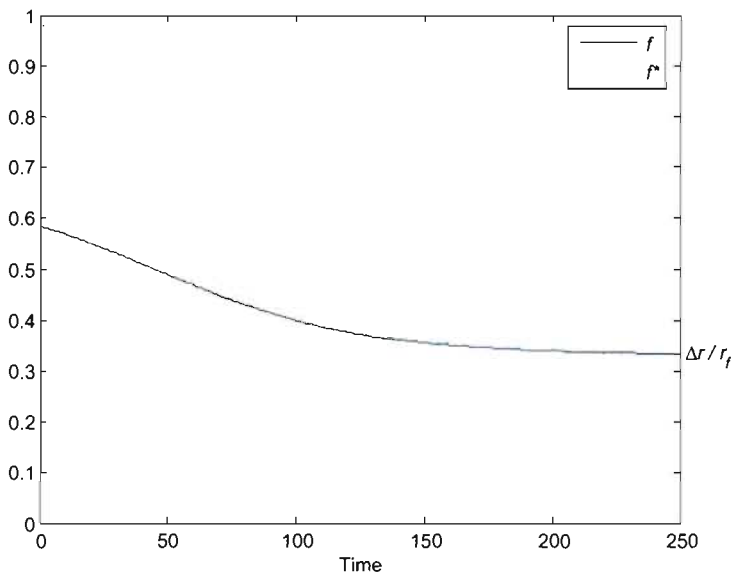

Figure 1.13: Comparison of the socially optimal and open-access treatment rates

CHAPITRE 2

MONOPOLY PRICING OF AN ANTIBIOTIC SUBJECT TO BACTERIAL RESISTANCE

2.1 Introduction

The quality of pharmaceutical drugs, notably antibiotics, depends on the efficacy of the treatment the drug can procure to the patient. In the case of antibiotics, treatment efficacy is affected by the infected individual's environment, in particular by the overall use that is and has been made within that environment. This externality is caused by the natural selection of bacterial strains that are resistant to antibiotic treatment.[1]

Pharmaceutical firms that produce an antibiotic are usually given temporary monopoly power through a patent, granted in order to recover the investment in R&D. The granting of this monopoly power ignores the fact that this also gives the firm some control over the level of efficacy of the drug and the level of infected population. The purpose of this paper is to study this aspect of the pricing policy of a monopolist whose market is protected by a patent and who is aware of the existing externalities.

Bacterial resistance to antibiotics has recently attracted the interest of economists. Most have put the emphasis on the determination of the socially optimal use of the antibiotic over time, ignoring the analysis of the market outcome. These include Laxminarayan and Brown (2001), Wilen and Msangi (2003), Rowthorn and Brown (2003) and Gersovitz and Hammer (2004). Very few have considered explicitly how the market will allocate the antibiotic use over time. Fischer and Laxminarayan (2005) is an exception, as are Herrmann and Gaudet (2007) and Mechoulan (2007). Fischer and Laxminarayan (2005) treat the problem as that of the sequential ex-

[1]By natural selection we understand the fact that the antibiotic-resistant bacterial strain will eventually dominate the infected population when a relatively intensive use is made of the antibiotic over time. See Levy (1992) for a useful overview of the subject of antibiotic resistance.

ploitation by a monopolist of exhaustible resources pools (the stock of efficacy of the antibiotics) when a setup cost must be incurred to access the next pool of resource (the next antibiotic). They show that whether the monopolist exploits the efficacy of the existing antibiotic faster or slower, and hence introduces the new drugs sooner or later than is socially optimal, may depend on whether there are many or few new drugs left to be developed. Herrmann and Gaudet (2007) model a generic industry as composed of antibiotic producers that have open access to the common resource pool of antibiotic efficacy and compare the market outcome in this case to the social optimum. It is shown that, depending on the bio-economic parameters of the model, in particular the cost of production and the increase in the recovery rate that results from treatment, the steady-state level of antibiotic efficacy that results from the generic industry may be lower or higher than is socially optimal. Mechoulan (2007) shows that while a social planner prefers eradication of infection (if possible), a monopolist achieves a steady state with a positive level of infection. He concludes that extending patent rights may be socially desirable if the increase in resistance is sufficiently high.[2]

It is shown in this paper that a monopolist who benefits from a patent on the sale of an antibiotic, and who takes into account the effect of his sales on the efficacy of his antibiotic (the quality of his product) and on the evolution of the infected population (his market size), will tend to price so as to spend a period of time in the neighborhood of the steady-state price of an infinitely-lived monopolist. The length of the period of time in question will depend on the patent life. Thus, if the patent life is long enough, the price path will at first decrease towards the steady-state price of the infinitely-lived monopolist, remain in the neighborhood of this price (or possibly exactly on it) for an interval of time, and leave it as the end of the patent approaches. In that final phase, the monopolist acts more and more as a myopic monopolist, that is one who neglects the impact of his decision

[2]In a much earlier contribution, Tisdell (1982) has argued that a monopoly may result in a socially optimal use of the drug, given the externality that results from antibiotic use. More recently Horowitz and Moehring (2004) have argued, using a diagrammatic analysis, that antibiotic resistance will tend to increase when the patent on an antibiotic expires.

on the evolution of the antibiotic efficacy and the stock of infected population. As a result, price decreases until it reaches the price charged by a myopic monopolist, just as the patent expires. The industry is then taken over by generic producers, with open access to the stock of efficacy of the antibiotic, and the price jumps down to average cost. Whether the turnpike property just described is exact or not and what length of time is spent near or at the infinitely-lived monopoly price depends on the bio-economic parameters and on the length of the patent life.

The paper is structured as follows. In Section 2.2, the epidemiological and economic models are presented. The monopolistic programme is characterized in Section 2.3. Two benchmark cases, which are the myopic monopolist and the infinitely lived monopolist are also considered for comparison in that section. We conclude in Section 2.4.

2.2 The model

The model has an epidemiological and an economic component. The epidemiological component (the so-called SIS-model) is borrowed from the epidemiological literature (see for instance Bonhoeffer *et al.*, 1997). It has already been used before in the economics literature by, among others, Laxminarayan and Brown (2001), Wilen and Msangi (2003) and Herrmann and Gaudet (2007). The economic component involves the interaction of the monopolist (on the supply side) with a derived demand for the antibiotic first presented in Herrmann and Gaudet (2007). We present the epidemiological model and the demand side of the economic component in what follows.

2.2.1 The epidemiological model

We assume that there is only one antibiotic treatment available to fight a particular infection. The infected population (I) is made up of those suffering from a drug-susceptible version of the infection (I_w) and those suffering from the drug-resistant version (I_r), both versions being naturally present in the system. The

problem of antibiotic resistance arises as the bacterial strain causing the drug-resistant version of the infection becomes predominant in the system, since the drug-susceptible bacterial strain clears at higher rate under antibiotic treatment. This effect is generally referred to as *natural selection*, on which we will concentrate here.[3] In such a context, an appropriate measure of antibiotic treatment efficacy (w) is the ratio of the population being infected with the drug-suspectable version to the overall infected population, *i.e.* $w = I_w/(I_w + I_r) = I_w/I$.

We assume the overall population to be constant and equal to N. The healthy population is then given by $S = N - I$. Let β be the rate of transmission of the infection between the healthy and the infected population. The SIS-model assumes that the rate of addition at time t to the infected population, either drug-resistant or drug-susceptible, is given by $\beta S(t)I_r(t)$ and $\beta S(t)I_w(t)$ respectively. The infected individuals may recover naturally, that is without taking the antibiotic. We denote the natural recovery rates from the drug-resistant and the drug-susceptible infection by r_r and r_w respectively. If all the infected individuals are treated with the antibiotic, the rate of recovery of those infected with the drug-resistant strain remains unchanged, while the rate of recovery of those infected with the drug-susceptible strain increases to $r_w + r_f$. If a fraction $f \in [0, 1]$ of the infected population is being treated with the antibiotic, the rate of recovery of those infected with the drug-susceptible strain will be $r_w + fr_f$. Hence the total infected population decreases at the rate $r_r I_r(t) + (r_w + fr_w)I_w(t)$.

The population dynamics can be summarized by the following system of differ-

[3] Antibiotic resistance may not only be caused by natural selection, but also by the mutation of drug-susceptible strains when being continually in contact with the antibiotic, or by the transfer of plasmids, *i.e.* genetic material transferred from resistant towards susceptible strains and containing information on how to be resistant. See for instance Levy (1992).

ential equations:

$$\begin{aligned} \dot{I}_w &= (\beta S - r_w - f r_f) I_w \\ \dot{I}_r &= (\beta S - r_r) I_r \\ \dot{S} &= -\dot{I} = -\dot{I}_w - \dot{I}_r. \end{aligned} \tag{2.1}$$

Note that the evolution of the healthy population ($\dot{S}$) is the complement of the evolution of the infected population ($\dot{I}$), since we have assumed the overall population to be constant.[4] Using this fact and the definition of antibiotic efficacy, we can rewrite system (2.1) as:

$$\dot{w} = w(1-w)[\Delta r - r_f f] \tag{2.2}$$

$$\dot{I} = I(\beta(N-I) - r_r + w[\Delta r - r_f f]) \tag{2.3}$$

where $\Delta r = r_r - r_w$ measures what is called in the epidemiological literature the fitness cost of resistance. The fitness cost can be understood as an opportunity cost of the resistant bacterial strains: they remain unaffected by antibiotic treatment, but this ability comes at the cost that they clear at a higher rate than drug-susceptible strains in the absence of antibiotic treatment.

We can now point out two important effects in the biological system that are apparent in equation (2.2): a positive fitness cost Δr implies renewability of the resource of antibiotic efficacy (fitness cost effect), while the additional recovery rate r_f helps clear drug-susceptible infections, leading potentially to the dominance of the drug-resistant version of the infection (natural selection effect). If a fraction $f = \Delta r / r_f$ of the infected population is treated with the antibiotic, those two effects cancel out. For all other admissible values of f, either one effect dominates,

[4]Biological parameters must be such that less individuals become infected than are susceptible to infection, thus ruling out that the overall system is dominated by infection. Assume the extreme case that no recovery from infection occurs: $r_w = r_r = r_f = 0$. Then the overall increase in infection is given by $\beta S(I_r + I_w) = \beta S I$ and must satisfy $\beta < 1/I$. For values of infection close to N we must have $\beta < 1/N$ which represents a sufficient condition that no more individuals become infected than are susceptible to infection if recovery rates satisfy $r_w, r_r, r_f \geq 0$.

leading to an increase or decrease in the level of antibiotic efficacy. We will assume throughout the paper that $\Delta r/r_f < 1$, so that both the fitness cost effect and the natural selection effect are apparent in the system.

There exist three steady-state configurations to the epidemiological dynamics described by (2.2) and (2.3). Let w^{SS} and I^{SS} denote the steady-state values of w and I respectively. For any $f \neq \Delta r/r_f$, we have $\dot{w} = 0$ for $w = 0$ or $w = 1$ and there are two distinct steady states, given by:

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_r}{\beta}, 0\right) \quad \text{and} \tag{2.4}$$

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_w - r_f f}{\beta}, 1\right) \tag{2.5}$$

For $f = \Delta r/r_f$, we have $\dot{w} = 0$ for any value of w and hence all

$$(I^{SS}, w^{SS}) = \left(\frac{\beta N - r_r}{\beta}, w \in [0,1]\right) \tag{2.6}$$

constitute steady states. We will assume throughout $\beta N - r_r > 0$ and $\beta N - r_w - r_f > 0$, thus guaranteing the existence of positively valued steady states for I.[5]

If the treatment rate f were to remain *constant* over time, then, in order to reach the steady state at which $w^{SS} = 1$, the fraction, say f_1, of the infected population being treated must satisfy $f_1 < \Delta r/r_f$. The steady state $w^{SS} = 0$ will be reached if a fraction, say f_2, gets treatment over time with $f_2 > \Delta r/r_f$. For the corresponding steady-state levels of the infected population, this implies

$$\frac{\beta N - r_r}{\beta} < \frac{\beta N - r_w - r_f f_1}{\beta}$$

Thus the steady state at which antibiotic efficacy reaches its upper bound ($w^{SS} = 1$), corresponds to a relatively higher level of the infected population than the

[5]We rule thus out that infection may be eradicated from the system in steady state. Notice that the steady-state levels of infection are increasing in the contagion rate β and decreasing in the recovery rates.

steady state at which antibiotic efficacy is lowest ($w^{SS} = 0$). For an interior steady state of w, which is reached if a fraction, say f_3, of the infected population gets treatment, with $f_3 = \frac{\Delta r}{r_f}$, the steady-state level of infection is equal to $(\beta N - r_r)/\beta$.

A representative evolution of the state variables starting from an interior state (I_0, w_0) and corresponding to the cases f_1 and f_2 just described is illustrated in Figure 3.1. Figure 3.1 represents a phase diagram and shows the $\dot{I}$-isocline and the corresponding forces driving the system when away from the isocline (as indicated by the arrows) under the two different regimes corresponding to the treatment rates f_1 or f_2.[6] In the case of $f_1 < \Delta r/r_f$ the continuous lines apply, and the system tends to the steady state at which $w^{SS} = 1$, since the fitness cost effect dominates. In the case of $f_2 > \Delta r/r_f$ the dashed lines apply, and the system tends to the steady state at which $w^{SS} = 0$, since the natural selection effect of resistant bacterial strains dominates. For $f = \frac{\Delta r}{r_f}$, both effects cancel out so that the level of antibiotic efficacy remains constant and the system converges to a steady state as defined in (2.6).

The crucial point is that the dynamic system is non-stationary with respect to the treatment rate f. If f changes over time, the $\dot{I}$-isoclines will also change. Values of f closer to the critical value $\Delta r/r_f$ imply steeper $\dot{I}$-isoclines. If the sequence of f converges monotonously to $\Delta r/r_f$ from above or from below, the isoclines will pivot around the point $((\beta N - r_r)/\beta, 0)$ and the dynamic system will converge to an interior steady state.[7]

---

[6] Analytically, the $\dot{I}$-isocline is derived by setting $\dot{I} = 0$, which gives $I = 0$ or $w = \tilde{w}(I) = \frac{\beta(I-N)+r_r}{\Delta r - r_f f}$. For $f < \Delta r/r_f$, the isocline has a positive slope, while it is negative for $f > \Delta r/r_f$. If f equals the critical fraction $\Delta r/r_f$, the $\dot{I}$-isocline is a vertical line passing through I^{SS} as defined in (2.6).

[7] In Herrmann and Gaudet (2007), it is shown that the treatment rates under the open-access market outcome approach the critical value $\Delta r/r_f$ monotonously from above or below, depending on the parameters and the initial state of the system.

2.2.2 The demand

The market demand for the antibiotic is derived under two main assumptions. First, we assume that individuals are vertically differentiated with respect to their valuation θ of being in good health, the distribution function of which is $F(\theta)$ over the population N. Second, we assume that infected individuals do not know whether they suffer from the drug-resistant or the drug-susceptible versions of the disease. However, we assume that they know the current treatment efficacy of the antibiotic, $w(t)$, and the natural recovery rates from either infection. In such a context, the probability of recovering from infection without antibiotic treatment is $\pi(w) = wr_w + (1-w)r_r$.[8] With antibiotic treatment, recovery from infection will occur with a higher probability of $[\pi(w) + wr_f]$.

The gross utility derived from health considerations by the individual of type θ will therefore be given by:

$$u(\theta) = \begin{cases} \theta & \text{if in good health} \\ \pi(w)\theta & \text{if infected and not taking the antibiotic} \\ [\pi(w) + r_f w]\theta & \text{if infected and taking the antibiotic.} \end{cases}$$

Only infected individuals whose valuation of being in good health is sufficiently high will buy the antibiotic. Denote by $\tilde{\theta}$ the type who is indifferent between buying the antibiotic or not when infected. The value of $\tilde{\theta}$ is determined by:

$$\pi(w)\tilde{\theta} = [\pi(w) + r_f w]\tilde{\theta} - p$$

which means that

$$\tilde{\theta} = \frac{p}{r_f w}. \tag{2.7}$$

Thus infected individuals with $\theta \geq \tilde{\theta}$ will buy the antibiotic and those with $\theta < \tilde{\theta}$ will not. The fraction of the infected population willing to buy the antibiotic is

[8] The weighted sum $\pi(w)$ represents the probability of recovery if the spread of infection and the valuation of being in good health are independent events and no antibiotic is taken.

$[1 - F(\tilde{\theta})]$, and, since individual demand is unitary, total demand is given by:

$$Q = I\left[1 - F\left(\frac{p}{r_f w}\right)\right].$$

Therefore the inverse demand function is:

$$P\left(\frac{Q}{I}, w\right) = r_f w F^{-1}\left(1 - \frac{Q}{I}\right).$$

For simplicity, let us assume that θ is distributed uniformly over the population, with supports $[0, 1]$. The inverse demand function then becomes:

$$P\left(\frac{Q}{I}, w\right) = r_f w\left(1 - \frac{Q}{I}\right).$$

Notice that the intercept of the inverse demand is $r_f w$ and its slope is $r_f w/I$. The variable w can be viewed as an (endogenous) index of the quality of the drug, which can vary between zero and one, while I is the market size for the antibiotic. For $w = 0$, demand is identically zero. For a given value of the infected population, I, the inverse demand curve pivots upwards through the point $(Q, p) = (I, 0)$ as the quality of the antibiotic increases from zero to one and demand is at its highest when $w = 1$.

The ratio Q/I represents the fraction of the infected population treated and is thus equal to the parameter f in the dynamic constraints (2.2) and (2.3). The inverse demand function can therefore be rewritten as a function of the fraction of the infected population being treated and the efficacy of the antibiotic to give:

$$P(f, w) = r_f w(1 - f). \tag{2.8}$$

2.3 The monopolistic pricing behavior

We assume that a patent exists, assigning exclusive rights to a monopolistic firm to sell the antibiotic for an exogenously given period of time $T \in (0, \infty]$, after

which the antibiotic is sold by a generic industry.[9] A farsighted monopolist is characterized by the fact that he takes into account the impact of his current decisions on future levels of antibiotic efficacy and infection, and thus on the evolution of the quality of his product and its market size over time. Hence, the quality and market size of the antibiotic are determined endogenously in the system. The instantaneous profit function of the monopolist is given by $\Pi(t) = [r_f w(t)(1 - f(t)) - c]f(t)I(t)$, where c is the constant unit cost of the antibiotic. For ease of reference to the epidemiological model, we will treat the fraction of the infected population to which the antibiotic is sold, $f(t)$, as the control variable, and infer the market clearing price $p(t)$ from the inverse demand function. The objective function of the monopolist is given by:

$$\max_{\{0 \leq f(t) \leq 1\}} \int_0^T e^{-\rho t} \Pi(t) dt + V^g(T) \tag{2.9}$$

subject to the equations (2.2) and (2.3). The bequest function $V^g(T)$ accounts for the profits of the former monopolist once he has become one of the competitive producers of the generic industry after the expiration of the patent. Assuming that all generic producers have access to the same technology as the monopolist does, the equilibrium in that generic industry will be such that price equals the average production cost and economic profits are zero.[10] Hence $V^g(T) = 0$.

The current-value Hamiltonian associated to problem (2.9) is given by:

$$\begin{aligned} H(f, w, I, \mu, \lambda) &= [r_f w(1 - f) - c]fI \\ &\quad + \mu w(1 - w)[\Delta r - r_f f] + \lambda I(\beta(N - I) - r_r + w[\Delta r - r_f f]) \end{aligned}$$

[9] We thus abstract from the R&D process before the patent is granted. Kingston (2000) presents historical notes on the R&D of the first antibiotics, and addresses aspects related to the patenting process of antibiotics.

[10] Such a generic industry and the resulting evolution of antibiotic efficacy and infection are addressed in Herrmann and Gaudet (2007). In that paper, competitive producers have open access to the market of the antibiotic drug, and by this to the stock of efficacy. Producers enter the market up to the point when all economic rents have been dissipated. They thus behave in a myopic way.

and its derivative with respect to the control variable f is:

$$\frac{\partial H}{\partial f} = [r_f w(1-2f) - c]I - r_f w[\mu(1-w) + \lambda I], \tag{2.11}$$

where μ and λ are the shadow values associated to the level of antibiotic efficacy and the stock of infected population respectively.

The following conditions, as well as (2.2) and (2.3), are necessary for inter-temporal profit maximization:

$$\begin{aligned}
\frac{\partial H}{\partial f} &\leq 0, \quad \frac{\partial H}{\partial f} f = 0, \quad f \geq 0 \quad \text{or} \\
\frac{\partial H}{\partial f} &\geq 0, \quad \frac{\partial H}{\partial f}(1-f) = 0, \quad f \leq 1 && (2.12) \\
\dot{\mu} - \rho\mu &= (\Delta r - r_f f)[\mu(2w-1) - \lambda I] - r_f I(1-f)f && (2.13) \\
\dot{\lambda} - \rho\lambda &= \lambda[2\beta I - \beta N + r_r - w(\Delta r - r_f f)] \\
&\quad -r_f w(1-f)f + cf && (2.14) \\
\lim_{t\to T} e^{-rt} w(T) &\geq 0, \quad \lim_{t\to T} e^{-rt}\mu(T) \geq 0, \quad \lim_{t\to T} e^{-rt}\mu(T)w(T) = 0 && (2.15) \\
\lim_{t\to T} e^{-rt} I(T) &\geq 0, \quad \lim_{t\to T} e^{-rt}\lambda(T) \geq 0, \quad \lim_{t\to T} e^{-rt}\lambda(T)I(T) = 0 && (2.16)
\end{aligned}$$

Condition (2.12) is the first-order condition for the maximization of the Hamiltonian with respect to $f(t)$ at each instant t. It can never be optimal for the monopolist to sell the antibiotic to the overall infected population ($f = 1$). This makes current profits negative without generating compensating future profits. Indeed setting $f = 1$ inevitably decreases the level of antibiotic efficacy and infection, or at least decelerates the increase in the level of infection, and thus negatively affects the future quality and market size of the antibiotic. We will therefore necessarily have $\partial H/\partial f \leqq 0$. However, it may be optimal to have $f = 0$, thus postponing production and allowing antibiotic efficacy and infection to rise as fast as possible.

Conditions (2.13) and (2.14) are the arbitrage equations that determine the evolution of $\mu(t)$ and $\lambda(t)$ over time. Conditions (2.15) and (2.16) are the transversality conditions. In the case of a finite patent life, they state that whenever there

is a strictly positive stock of antibiotic efficacy or of the infected population left at the end of the patent lifetime ($w(T) > 0,\ I(T) > 0$), then that stock must be of no value to the non-myopic monopolist. The same reasoning applies in the limit as t tends to infinity in the case of an infinitely long lasting patent.

In the case of an interior solution, $(0 < f^m < 1)$, equation (2.12) can be written as:

$$r_f w(1 - 2f^m) = c + \frac{r_f w}{I}\left[\mu(1 - w) + \lambda I\right]. \tag{2.17}$$

Condition (2.17) states that the marginal revenue (the left-hand side of equation (2.17)) must be equal to the full marginal cost of treatment (the right-hand-side). Both shadow values will be positive. This reflects the fact that the stock of the infected population can be viewed as an "asset" by the monopolist, since it represents market size when the antibiotic is economically viable.

An interior solution f^m is represented graphically in Figure 2.3, where the solid and dotted lines represent the downward-sloping demand and marginal revenue function respectively. This figure shows a momentary view of the monopolist's choice given the dynamic system is in state (w, I) at time t. As in the standard static monopoly model, the monopolist will always serve a fraction such that demand is elastic, ruling out admissible values of f in the interval $(1/2, 1]$. The reason for this is the same as the reason why $f = 1$ cannot be an optimal policy for the monopolist. Incurring a loss at a current instant of time would have to be compensated by higher profits somewhere in the future. But this is not the case, since such a policy would lead to lower levels of quality and market size and thus cannot lead to higher profits. This implies that whenever $\Delta r/r_f \in [1/2, 1]$, the fitness cost effect dominates,*i.e.* the level of antibiotic efficacy will be increasing over time, as the optimal fraction f served by the monopolist will always be lower than $1/2$ (for $c > 0$). For $\Delta r/r_f \in [0, 1/2)$, the fraction served by the monopolist may be lower, equal or higher than the critical value of $\Delta r/r_f$, implying an increasing, constant or decreasing movement of antibiotic efficacy over time.

Before turning to the monopolist that benefits from a limited patent lifetime,

we will address two useful benchmark cases. The first is that of a monopolist who ignores the effect of his actions on the future state, which we will call a myopic monopolist. The second is that of an infinitely-lived monopolist.

2.3.1 The myopic monopolist

In this section we consider the pricing policy, and its impact on the dynamics of antibiotic efficacy and infection, when the antibiotic is sold by a myopic monopolist. The myopic monopolist maximizes the flow of discounted profits without taking into account the impact of his current decision, $f(t)$, on future levels of antibiotic efficacy, and on the future stock of the infected population. He thus attributes a zero shadow value to the quality and market size of the antibiotic, which implies $\mu(t) = 0$ and $\lambda(t) = 0$. Using this fact in equation (2.12), the first order condition for an interior solution can be written as:

$$r_f w(1 - 2f)I \;\; = \;\; cI. \tag{2.18}$$

Denote by $f^{\infty}(t)$ the fraction of the infected population buying the antibiotic when sold by a myopic monopolist, and by $p^{\infty}(t)$ the corresponding price. From condition (2.18) we obtain:

$$f^{\infty}(t) = \begin{cases} \frac{1}{2}\left(1 - \frac{c}{r_f w(t)}\right) & \text{, if } r_f w > c \\ 0 & \text{, otherwise.} \end{cases} \tag{2.19}$$

With the inverse demand function stated in (2.8), we get:

$$p^{\infty}(t) = \begin{cases} \frac{1}{2}\left(r_f w + c\right) & \text{, if } r_f w > c \\ r_f w & \text{, otherwise.} \end{cases} \tag{2.20}$$

If the antibiotic is economically viable, the myopic monopolist sells it to a positive fraction of the infected population and charges the corresponding market clearing price. If the antibiotic is not economically viable, he charges the choke price $r_f w$,

and does not sell at all. Both, the fraction of the infected population buying the antibiotic, $f^{\infty}(t)$, as well as the price charged by the myopic monopolist, $p^{\infty}(t)$, are increasing in the level of antibiotic efficacy, the quality aspect of the antibiotic, while $f^{\infty}(t)$ is decreasing and $p^{\infty}(t)$ is increasing in the unitary production cost c. Notice that they are both independent of the level of infection.

2.3.1.1 The steady states under myopic monopolistic pricing

Consider first the epidemiological steady state given by (2.4), at which the level of antibiotic efficacy is exhausted completely ($w^{SS} = 0$) and demand vanishes. Any positive production of the antibiotic would lead to losses for the myopic monopolist, so that the monopolist would find it optimal not to produce at all by setting $f^{SS} = 0$. The steady state would therefore be characterized by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(0, \frac{\beta N - r_r}{\beta}, 0\right) \tag{2.21}$$

With a positive production cost $c > 0$, this steady state can be ruled out. This is because the myopic monopolist, by setting $f^{\infty}(t) = 0$ whenever the antibiotic is not economically viable, allows the level of antibiotic efficacy to recover ($\dot{w} > 0$), and therefore it cannot reach its lower limit at which $w^{SS} = 0$.

In the epidemiological steady state given by (2.5), the quality of the drug is maximal. From (2.19), we find $f^{\infty} = (1 - c/r_f)/2$. Therefore, the steady state will be characterized by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(\frac{1}{2}\left(1 - \frac{c}{r_f}\right), \frac{\beta N - r_w - \frac{1}{2}(r_f - c)}{\beta}, 1\right). \tag{2.22}$$

Finally, steady states as defined in (2.6) occur when $f^{\infty} = \Delta r / r_f$, which is only optimal for the myopic monopolist whenever the level of antibiotic efficacy $w(t)$ satisfies:

$$\frac{\Delta r}{r_f} = \frac{1}{2}\left(1 - \frac{c}{r_f w(t)}\right). \tag{2.23}$$

Hence the unique steady state of this type is given by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(\frac{\Delta r}{r_f}, \frac{\beta N - r_r}{\beta}, \frac{c}{r_f - 2\Delta r}\right). \tag{2.24}$$

Notice that the steady-state configurations (2.22) and (2.24) are mutually exclusive. Which one is relevant depends on the bio-economic parameters of the model. To be more precise, if $c = r_f - 2\Delta r$, they are indistinguishable at $w^{SS} = 1$. Whenever $c < r_f - 2\Delta r$, then (2.24) must be the relevant steady-state configuration, because this is incompatible with (2.19) when evaluated at $w^{SS} = 1$. Whenever the parameters satisfy $c/(r_f - 2\Delta r) > 1$ then (2.22) must be the relevant steady-state configuration, because it must then be the case that $w^{SS} = 1$ and $f^{SS} = (1 - c/r_f)/2 < \Delta r/r_f$.[11]

2.3.1.2 The transition to steady state under myopic monopolistic pricing

The stock of infected population $I(0) = I_0 \in (0, N]$ and the stock of antibiotic efficacy $w(0) = w_0 \in (0, 1)$ are given exogenously in the system at time $t = 0$. From the initial state (I_0, w_0) the system will tend asymptotically to the relevant steady-state configuration. Let I and II denote states for which $w > w^{SS}$ and III and IV denote states for which $w < w^{SS}$, with states I and III lying to the left of the $\dot{I} = 0$ isocline, while states II and IV lie to its right in (I, w)-space. This is shown in Figure 2.2, where the $\dot{I} = 0$ isocline is represented for $f^{\infty} = \Delta r/r_f$.[12] The evolution of the levels of antibiotic efficacy $w(t)$ and infection $I(t)$ depends on the fraction of the infected population $f^{\infty}(t)$ to which the myopic monopolist

[11] We have implicitly assumed that $r_f - 2\Delta r > 0$, which guarantees a positive value for w^{SS} in steady state (2.24). The condition can be rewritten as $1/2 > \Delta r/r_f$. If it is not satisfied, only steady-state configuration (2.22) with $w^{SS} = 1$ is relevant. This is because the myopic monopolist behaves like a static one, and thus always sells on the elastic part of the demand curve, implying $f^{\infty} < 1/2 < \Delta r/r_f$ for $c > 0$ in that case, and thus $\dot{w} > 0$ and $w^{SS} = 1$.

[12] The $\dot{I} = 0$ isocline is non-stationnary. Remind footnote 6. In Figure 2.2, we represent the steady-state configuration of type (2.24). The analysis however also applies to the steady-state configuration with $w^{SS} = 1$ where the initial state (I_0, w_0) is either of type III and IV.

sells the antibiotic over time, or equivalently, on the price charged $p^{\infty}(t)$. We first concentrate on the characterization of $f^{\infty}(t)$, $p^{\infty}(t)$ and $w(t)$, before addressing the evolution of the level of infection and the transition to steady state in general. Differentiating equations (2.19) and (2.20) with respect to time for any steady-state configuration gives:

$$\dot{f}^{\infty} = \frac{c}{4r_f}(2\Delta r - r_f)\frac{1-w}{w^2}\left[w - \frac{c}{r_f - 2\Delta r}\right] \tag{2.25}$$

$$\dot{p}^{\infty} = \frac{r_f^2 w^2}{c}\dot{f}^{\infty} \tag{2.26}$$

Suppose for now the antibiotic to be economically viable. If the steady-state configuration is of type (2.22), we have $w(t) \leqq w^{SS} = 1$ with $t \in [0, \infty)$ so that:

$$f^{\infty}(t) = \frac{1}{2}\left(1 - \frac{c}{r_f w(t)}\right) < \frac{1}{2}\left(1 - \frac{c}{r_f}\right) < \frac{\Delta r}{r_f},$$

implying by equation (2.2) the level of antibiotic efficacy $w(t)$ to be increasing over time for initial states of types III and IV. This steady-state configuration occurs only when $c/(r_f - 2\Delta r) > 1$ or $r_f - 2\Delta r < 0$ and thus implies, by equations (2.25) and (2.26), that the fraction served as well as the price charged by the myopic monopolist must be increasing over time. This is because the increase in quality shifts the demand and marginal revenue curves upwards (for any given level of infection). As the level of antibiotic efficiency approaches its upper bound, the increase in the treatment rate and in the price slow down as $\dot{f}$ and $\dot{p}$ tend to zero.

If the steady-state configuration is of type (2.24), we have for any $t \in [0, \infty)$:

$$f^{\infty}(t) = \frac{1}{2}\left(1 - \frac{c}{r_f w(t)}\right) \gtreqless \frac{\Delta r}{r_f} \quad \Leftrightarrow \quad w(t) \gtreqless \frac{c}{r_f - 2\Delta r} = w^{SS},$$

where w^{SS} is the steady-state level of antibiotic efficacy in that configuration. Hence, the fraction $f^{\infty}(t)$ is larger, smaller or equal to the critical fraction $\Delta r/r_f$ depending on whether the current level of antibiotic efficacy $w(t)$ is larger, smaller or equal to the long-run steady-state level w^{SS}. It follows that $w(t)$ is decreasing

over time when the initial state is of type I or II, and increasing when it is of type III or IV. If $w_0 = w^{SS}$, then the level of antibiotic efficacy remains constant over time ($\dot{w} = 0$). Convergence of $w(t)$ to steady state will occur monotonously (from above or from below). As $w(t)$ approaches the long-run steady state w^{SS}, $\dot{f}$ and $\dot{p}$ tend to zero, and the fraction served must tend to the critical value of $\Delta r/r_f$. When the steady-state value for antibiotic efficacy is reached, $w^{SS} = c/(r_f - 2\Delta r)$, we must simultaneously have $f^{\infty} = \Delta r/r_f$ from equation (2.23) and $\dot{f^{\infty}} = 0$ from equation (2.25).

We have seen so far that the evolution of the variables w, f^{∞} and p^{∞} can be characterized independently from the level of infection, or the market size of the antibiotic, I, the evolution of which we now consider. Equation (2.3), which determines the evolution of the level of infection, can be rewritten, after substituting for f^{∞} and rearranging, as:

$$\frac{\dot{I}}{I} = \beta(I^{SS} - I) + \frac{1}{2}(r_f - 2\Delta r)\left[w^{SS} - w\right] \tag{2.27}$$

where I^{SS} and w^{SS} are defined as in the relevant steady-state configuration (2.22) or (2.24). Equation (2.27) states that the relative increase in the level of infection is a function of the relative distance of the state variables from their long-run steady-state levels. Suppose $(r_f - 2\Delta r) > 0$ such that no steady-state configuration can be excluded from the outset. Then, unambiguously, $\dot{I} < 0$ as long as the state is of type II and $\dot{I} > 0$ if of type III as can be seen from equation (2.27). The evolution of the level of infection can be either in- or decreasing if the state is of type I or IV. Suppose that $I_0 = I^{SS}$ and $w > w^{SS}$. Then, by equation (2.27), $\dot{I}(0) < 0$, and the level of infection falls below its steady-state level, such that $I^{SS} - I > 0$ initially (type I). The level of infection will decrease, as will the difference $I^{SS} - I$, while $w^{SS} - w(< 0)$ decreases as shown earlier. [13]

[13]We exclude the possibility that the decrease in the level of infection eventually leads to its eradication from the biological system. A sufficient condition for this is that the $\dot{I} = 0$ isocline shown in Figure 3.1, when evaluated at $f_2 = 1$ has an intercept greater than $w = 1$.

The first term on the right-hand side of equation (2.27) eventually cancels the second one, with $\dot{I} = 0$ at that point of time, after which $\dot{I} > 0$, and both $I^{SS} - I$ and $w^{SS} - w$ decrease. This continues until a steady-state is reached. The overshooting of the level of infection which may occur when departing from an initial state of type I is reversed when departing from a state of type IV.[14]

2.3.2 The infinitely-lived monopolist

The case of an infinitely-lived monopolist ($T = \infty$) represents another benchmark for the analysis of how a non-myopic monopolist subject to a patent manages antibiotic efficacy and infection over time. As it turns out, the infinitely-lived monopolist tends to achieve higher levels of antibiotic efficacy over time and in steady state than the myopic monopolist. It also prevents the level of infection from falling as sharply below its steady-state value as in the myopic outcome.

2.3.2.1 The steady states

Setting $\dot{w} = \dot{I} = \dot{\mu} = \dot{\lambda} = 0$ generates the set of steady states that may be reached when the antibiotic is sold by a non-myopic monopolist. The epidemiological steady state of type (2.4), at which the antibiotic is completely inefficient ($w = 0$), and which we found could not be reached under the myopic monopolistic programme, cannot be reached either under the non-myopic programme. As before, the monopolist would incur losses by selling the antibiotic when its efficacy is below the economic viability level ($w < c/r_f$). He would prefer not to sell at all ($f = 0$), allowing the level of antibiotic efficacy to increase.

[14] If $c/(r_f - 2\Delta r) > 1$ holds, the level of antibiotic efficacy tends to its upper bound. The steady state is then as defined in (2.22). Unambiguously, $\dot{I} > 0$ for states of type III, while the overshooting pattern may occur for states of type IV ($I > I^{SS}$ temporarily). The same steady state is reached if the condition $r_f - 2\Delta r < 0$ holds, and $\dot{I} < 0$ for states of type IV and the overshooting pattern with respect to the level of infection may then occur for initial states of type III.

The discussion in the text shows that the system will reach the neighborhood of the relevant steady state, and in connection with the local stability of that steady state (which can be shown by standard methods of linearizing the dynamic system around the relevant steady state), establishes its *global* stability under the myopic monopolistic programme.

In the epidemiological steady state given by (2.5), antibiotic efficacy is at its upper bound ($w = 1$). Replacing $w = 1$ in (2.12) and in (2.14) with $\dot{\lambda} = 0$ yields two equations in f and λ, the unknowns of which can be solved for (see the Appendix). At this steady state we will therefore have:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(\frac{a}{2} - \sqrt{\left(\frac{a}{2}\right)^2 - b}, \frac{\beta N - r_w - r_f f}{\beta}, 1 \right) \tag{2.28}$$

where a and b are determined in the Appendix as:

$$\begin{aligned} a &= \frac{2}{3r_f}[\rho + \beta N - r_w + r_f - c] \\ b &= \frac{\left(1 - \frac{c}{r_f}\right)(\rho + \beta N - r_w)}{3r_f}. \end{aligned}$$

Finally, there is a unique steady state of the type characterized by (2.6). This steady state is shown in the Appendix to be given by:

$$(f^{SS}, I^{SS}, w^{SS}) = \left(\frac{\Delta r}{r_f}, \frac{\beta N - r_r}{\beta}, -\frac{B}{2A} + \sqrt{\frac{c}{A} + \left(\frac{B}{2A}\right)^2} \right) \tag{2.29}$$

where

$$\begin{aligned} A &= \Delta r(r_f - \Delta r)\frac{\beta N - r_r}{\rho(\rho + \beta N - r_r)} \\ B &= (r_f - 2\Delta r) - \Delta r\frac{r_f - \Delta r}{\rho} + \frac{\Delta r c}{\rho + \beta N - r_r}. \end{aligned}$$

Steady-state configurations (2.28) and (2.29) are mutually exclusive. In fact, when $w^{SS} = 1$ in (2.29) they are indistinguishable with respect to the level of antibiotic efficacy. This will occur when the bio-economic parameters satisfy

$$c = \tilde{c}(r_f) = \frac{-\Delta r\left[2(\beta N - r_r + \rho) - \Delta r\right]}{\beta N - r_r + \rho - \Delta r} + r_f, \tag{2.30}$$

which can be derived from setting $w^{SS} = 1$ and solving for the cost c. For $c \leq$

$\tilde{c}(r_f)$, the monopolistic steady state will be defined as in (2.29), while for $c > \tilde{c}(r_f)$ the steady state will be defined as in (2.28). Equation (2.30) represents a positively sloped straight line in $(r_f, c)-$space, the intercept of which may be positive, negative or zero.[15]

Figure 2.4 shows the line $\tilde{c}(r_f)$ for the case $\beta N - r_r + \rho - \Delta r > 0$, as well as the economic viability condition $c = r_f$ in the $(r_f, c)-$space.[16] For parameter values implying a positive intercept of $\tilde{c}(r_f)$, the steady-state configuration is always as specified in (2.29) when the antibiotic is economically viable, as assumed from the outset.

Ceteris paribus, for any given value of the cost c, higher values of the additional recovery rate r_f (and thus lower values of the critical fraction $\Delta r/r_f$) imply an interior steady-state level of antibiotic efficacy (configuration (2.29)). This is because the optimal fraction of the infected population served by the monopolist, f, as defined in (2.12), is then higher than the critical fraction $\Delta r/r_f$, which leads to a decreasing level of antibiotic efficacy and makes the steady-state configuration given by (2.28) unattainable. Stated differently, a high value of the additional recovery rate r_f implies a relatively high selective pressure on the drug-sensitive version of the infection (I_w), rendering the achievement of the maximum value of antibiotic efficacy ($w^{SS} = 1$) impossible.

Comparing the interior steady-state configurations of the myopic and the non-myopic monopolist as defined in (2.24) and (2.29) shows that both the fraction of the infected population that buys the antibiotic, f^{SS}, and the level of the infected population, I^{SS}, are identical. The steady-state levels of antibiotic efficacy differ however in this steady-state configuration. It can be shown, assuming $c/(r_f - 2\Delta r) < 1$, that the non-myopic steady-state level w^{SS} is always higher than the

[15]Whenever the denominator in the right-hand side of equation (2.30) is positive, the ordinate is negative. For a negative denominator, the ordinate may be positive, negative or zero, depending on whether $I^{SS} = \frac{\beta N - r_r}{\beta} \gtreqless \frac{\Delta r - 2\rho}{2\beta}$.

[16]Admissible values of the additional recovery rate r_f lie in the interval $(\Delta r, \beta N - r_w)$, which assures $\Delta r/r_f < 1$ and a strictly positive steady-state value for infection in configuration (2.28).

one reached under the myopic programme:

$$w^{SS} > \frac{c}{r_f - 2\Delta r} \equiv w_\infty^{SS}.$$

The locus of parameter configurations such that $w_\infty^{SS} = 1$ is given by $c = r_f - 2\Delta r$ and is also shown in Figure 2.4.

2.3.2.2 The transition to steady state

Because of the complex nature of the dynamic system involved in the monopolistic optimal control problem, numerical simulations have been used to explore the transition to the steady state.[17] Those simulations show that depending on the bioeconomic parameters of the model, the system may tend to the steady state as defined in (2.28), for which $w^{SS} = 1$, or to the "interior" steady state as defined in (2.29), for which $f^{SS} = \Delta r / r_f$. In what follows, we concentrate our analysis on the production cost c and the additional recovery rate r_f, and refer to the classification of steady states as presented in Figure 2.4.

Case A: $f^{SS} = \frac{\Delta r}{r_f}$

In this case, the parameter configuration of c and r_f is such that they fall below the line $\tilde{c}(r_f)$, and the steady state reached is interior for the monopolist as defined in (2.29).[18] Starting from the four different types of initial states (I_0, w_0), indicated by I to IV, the trajectories of the state variables and of the evolution of the monopolistic treatment rate are shown in Figures 2.5 and 2.6 respectively. For comparison, we have also drawn the paths resulting under the myopic programme. In Figures 2.5 and 2.6 non-myopic paths are indicated by thicker lines. All state paths have in common that they converge towards their respective steady state, indicating that the dynamic system is stable under both regimes, with the non-

[17] We make use of a standard value function iteration algorithm, as proposed in Judd (1998, page 413) for a discrete time version of the model.

[18] Parameters used for that simulation are $\beta = 0.6$, $N = 1$, $r_r = 0.17$, $r_w = 0.15$, $\Delta r = 0.02$, $r_f = 0.3$, $c = 0.27$ $\rho = 0.03$.

myopic steady-state level of antibiotic efficacy being greater than the myopic one, *i.e.* $w^{SS} > w_{\infty}^{SS}$.

Consider the paths departing from initial states of types III and IV, which lie below the economic viability level c/r_f, such that no antibiotic is sold initially under any regime. Since the evolution of antibiotic efficacy $\dot{w}$ is independent of I, myopic and non-myopic state paths departing from an initial state of types III and IV coincide as long as $f = 0$. When the antibiotic has become economically viable, the myopic monopolist immediately starts selling to a fraction f^{∞} as defined in (2.19), which again does not depend on the level of infection. The two state and control paths therefore continue to coincide and converge to the steady state (2.24). That convergence occurs with a slight overshooting in the level of infection as described in section 2.3.1.2. The non-myopic monopolist reaches the economic viability level at the same time as the myopic one. However, he starts selling later as can be seen from Figure 2.6.[19] This is because he attributes positive shadow values to the levels of antibiotic efficacy and infection, implying a full marginal cost higher than c, and waits for the quality to rise even more in order to compensate for the full marginal cost. For the non-myopic monopolist, the positive overshooting pattern is more pronounced than for the myopic one, as he has an interest in facing a 'high' demand in the future.

Consider now the initial states of type I and II in Figure 2.5, characterized by a high level of antibiotic efficacy and a relatively low (type I) or high (type II) level of infection. When departing from an initial state of type I, the monopolist manages the level of infection (the market size), in such a way as to have it increase faster than the myopic monopolist while keeping high values of antibiotic efficacy. Comparing the treatment rates in Figure 2.6 under both regimes in this case reveals that the non-myopic monopolist sells to a low fraction of the infected population initially, thus allowing the level of infection to increase relatively fast.[20] When

[19]Trajectories of the treatment rates completely coincide for initial states III and IV for the non-myopic monopolist, as the state paths (I, w) departing from initial states III and IV join each other before the antibiotic becomes economically viable and are identical thereafter.

[20]The level of antibiotic efficacy also increases initially, something which cannot occur under

departing from an initial state of type II, the non-myopic monopolist serves a decreasing fraction, at a lower level than the myopic monopolist (initially). This allows him to soften the overshooting of infection below its steady-state level, thus assuring a higher market size over time.

Figure 2.7 displays the evolution of prices and the level of antibiotic efficacy when the initial state is of type II. Prices are decreasing under both regimes and reflect the evolution of antibiotic efficacy. We have also drawn the hypothetical price $p^H(t)$, that a myopic monopolist would charge if he were to be at the same state (I, w) as the non-myopic one. The prices charged by the non-myopic monopolist would be higher than those charged by the hypothetical myopic monopolist, thus restricting the fraction of the infected population to which the antibiotic is sold, and finally leading to a higher steady-state value of antibiotic efficacy.

Case B: $w^{SS} = 1$

In this case, bio-economic parameters c and r_f belong to the region lying between the line $\tilde{c}(r_f)$ and the economic viability line $(c = r_f)$, as depicted in Figure 2.4.[21] Figures 2.8 and 2.9 show the convergence to steady state for the state variables (I, w) and the control f for the non-myopic monopolist. The trajectory for the myopic monopolist are also shown. The level of antibiotic efficacy in initial states of types I and II is set at c/r_f, so that the antibiotic is just economically viable, whereas in initial states of types III and IV it is not economically viable. When departing from initial states of types I and II, the myopic monopolist starts selling immediately, while the non-myopic monopolist waits some time before doing so. This is due to the fact that the non-myopic monopolist faces at each instant of time a full marginal cost which is higher than the marginal cost of production leading to $\partial H/\partial f < 0$ initially. When $\partial H/\partial f = 0$ the non-myopic monopolist starts selling. For a given level of antibiotic efficacy, equalizing the higher full

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the myopic regime

[21] Parameters used for this simulation are identical to the ones used in the former simulation, exception being the cost of production $c = 0.27$.

marginal cost to the marginal revenue can only occur at a treatment rate which is lower than under the myopic outcome. As a result, antibiotic efficacy evolves at a higher level in the non-myopic outcome than in the myopic outcome, as can be seen from the trajectory of the level of antibiotic efficacy depicted in Figure 2.10 for the case that the initial state is given by II. The pricing scheme under the myopic and non-myopic regimes are also depicted in Figure 2.4. Prices reflect the evolution of antibiotic efficacy under both outcomes. The level of antibiotic efficacy increases faster towards $w^{SS} = 1$ when managed by the non-myopic monopolist, who charges higher prices than would a hypothetical myopic monopolist.

2.3.3 Finite patent life: $T < \infty$

Consider now the case of a patent of finite duration ($T < \infty$). The antibiotic is then sold by a monopolist during the life of the patent and by a generic industry afterwards. Since the monopolist knows that he will make zero economic profits after the expiration of the patent, he will attach no importance to the levels of antibiotic efficacy and infection that are left for the generic industry. At time T, he should thus attribute zero value to the levels of antibiotic efficacy and infection, if positive, and behave like a myopic monopolist. This is indeed the case, as can be seen from the transversality conditions (2.15) and (2.16). As the monopolist cannot operate below the economic viability level, c/r_f, nor eradicate infection from the epidemiological system, we must have $w(T) > 0$ and $I(T) > 0$, which from equations (2.15) and (2.16) implies:

$$\mu(T) = \lambda(T) = 0. \tag{2.31}$$

Hence, at the instant the patent expires, the pricing policy of the non-myopic monopolist must be identical to the myopic one defined in (2.19) and (2.20) and evaluated at state $(I(T), w(T))$. The shadow values will evolve continuously over time as described by equations (2.13) and (2.14) and will reach $\mu(T) = \lambda(T) = 0$

at time T.[22] At T, we can calculate the rate of change in the shadow values making use of (2.31) and obtain:

$$\begin{aligned} \dot{\mu}(T) &= -r_f I(T)(1-f(T))f(T) < 0, \\ \dot{\lambda}(T) &= -r_f w(T)(1-f(T))f(T) < 0. \end{aligned}$$

Due to the continuity in the evolution of the shadow values, we can conclude that the shadow values are positive and decreasing at least during a time period before the patent's expiration. This implies a decreasing full marginal cost for given levels of antibiotic efficacy and of the infected population, leading to an increase in the fraction of the infected population served towards the end of the patent life time in order to satisfy equation (2.12). The non-myopic monopolist thus behaves "more and more myopically" as the patent approaches its expiration date.

In our numerical analysis we refer again to two different scenarios which depend on the bio-economic parameters and the implied infinite-horizon steady-state configurations as described in section 2.3.2.1. If the parameter configuration is such that the interior steady state, as defined in (2.29), were to be reached in the infinite horizon problem, the non-myopic monopolistic programme is characterized by a turnpike property with the steady state (I^{SS}, w^{SS}) serving as the turnpike. If T, the length of the patent life, is sufficiently large, then the turnpike is "exact": the system reaches the steady state and remains there for a finite period of time before leaving it at some point before the patent expires.

Figure 2.11 and Figure 2.12 show the trajectories of antibiotic efficacy and infection, as well as the fraction of the infected population that buys the antibiotic when it is sold by a non-myopic monopolist. We also plot the outcome under the myopic monopolistic regime for purpose of comparison. The approach to the steady state is identical to that of the infinite horizon problem. At the interior steady state

[22] Jumps in the shadow values could be caused by binding constraints on the state variables. This can however be excluded as $w^{SS} = 0$ and $w^{SS} = 1$ cannot be reached in finite time and infection cannot be eradicated nor dominate the whole system because of the parameter values assumed in section 2.2.1.

(I^{SS}, w^{SS}), we have $f^{SS} = \Delta r/r_f$. What is of interest in the case of a finite patent life is the monopolistic policy once the path leaves the turnpike. The monopolist then sells to an increasing fraction of the infected population, $f(t) > f^{SS}$, as can be seen in Figure 2.12. This leads to a decrease in the levels of antibiotic efficacy and infection (the state trajectory moves in the south-western direction in Figure 2.11), and thus to a decreasing price as shown in Figure 2.13. This occurs because the monopolist associates lower shadow values to the quality aspect of the drug (w) and to the market size (I), as he knows that he will make zero profits after the patent has expired and tends to behave more and more like a myopic monopolist. At time T, the non-myopic monopolist behaves exactly like a myopic monopolist and charges the myopic price as defined in (2.20). To see this, consider the prices charged by a hypothetical myopic monopolist $p^H(t)$ who faces the same state as the non-myopic one in Figure 2.13. It is at T that the pricing schemes $p(t)$ and $p^H(t)$ represented by the thin continuous and dotted lines join.

For an insufficiently long patent life, the turnpike property of the monopolistic programme is not exact: the path approaches the steady state (I^{SS}, w^{SS}) and remains in its neighborhood for a finite period of time before leaving to satisfy the transversality conditions. This is shown in Figure 2.14, where we depict the trajectories of the fraction of the infected population buying the antibiotic as an example. The heavy lines indicate the treatment rates $f(t)$ for the non-myopic monopolist, which approach the steady-state level of $\Delta r/r_f$ from above when departing from initial states of type I and II, and which approach it from below, when departing from initial states of type III and IV.[23] In all cases, the treatment rate $f(t)$ increases towards the end of the patent and trajectories of $f(t)$ eventually join and reach the same level, which is higher than the critical level $(\Delta r/r_f)$.[24]

[23]The approach is monotonous in all cases, except when the initial state is of type I. In that case, the initial level of infection is low, while the level of antibiotic efficacy is high. This leads the monopolist to initially sell the antibiotic to relatively low fractions $(f(t) < \Delta r/r_f)$, allowing the market size and quality of the antibiotic to increase.

[24]The question arises of what is the critical patent life T for an exact turnpike to exist. And in such a case, when is the turnpike reached, and when is it left again. The critical value of T is determined implicitly by the necessary conditions (2.12) to (2.16) characterizing the profit-

When the patent expires, the generic industry takes over, and an upward jump in the level of $f(t)$, accompanied by a fall in price occur. As the full marginal cost faced by the monopolist is equal to c at time T, the corresponding monopolistic price $p^m(T)$ is necessarily higher than the price of the generic industry which is given by $p^g = c$.

Finally, consider the parameter configuration under which the infinitely-lived monopolist would reach the steady state of type (2.28). In this case, if the patent life is sufficiently long, the system is again characterized by an exact turnpike, with the level of antibiotic efficacy reaching its upper bound, $w = 1$. The level of w will remain unchanged, even after leaving the turnpike in order for the costate variables to satisfy the transversality conditions. The decrease in the full marginal cost, which occurs after leaving the turnpike, is due strictly to the decrease in the shadow value of infection, λ. This can be seen from equation (2.17), which simplifies for $w = 1$ to

$$r_f(1 - 2f^m(t)) = c + r_f\lambda(t).$$

As in the previous case, a falling full marginal cost is accompanied by an increase in the treatment rate, leading to a decrease in the level of infection. What differs under this parameter configuration, which is characterized by a marginal production cost (c) that is high relative to the increase in the recovery rate (r_f), is that the generic industry now inherits a perfectly effective antibiotic drug. The problem of antibiotic resistance is non-existing after the generic industry takes over.

One should however not interpret this result as arguing in favor of the monopolistic industry from a social optimum point of view. The upper bound of antibiotic

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maximizing monopolistic programme. Suppose T to be sufficiently long such that a turnpike exists. Denote by t_1 and t_2 the points of time when the turnpike is reached, and when it is left again. In order to obtain those dates, one would have to solve the differential equations $\dot{w}$, $\dot{I}$, $\dot{\mu}$, $\dot{\lambda}$ satisfying condition (2.12) and the boundary conditions $w(0) = w_0$, $I(0) = I_0$, $w(t_1) = w(t_2) = w^{SS}$, $I(t_1) = I(t_2) = I^{SS}$, $\mu(t_1) = \mu(t_2) = \mu^{SS}$, $\lambda(t_1) = \lambda(t_2) = \lambda^{SS}$ and $\mu(T) = 0$ as well as $\lambda(T) = 0$. One would first solve for t_2, and then for t_1. The critical value for a turnpike to exist, $\bar{T}$, is then defined by $\bar{T} = t_1 + t_2$. All those conditions should suffice to determine a unique trajectory of the state, co-state and control variables. The analytical resolution of the dynamic system however represents arduous task.

efficacy may also be attained by a generic industry under similar parameter configurations (see Herrmann and Gaudet, 2007). It is the relatively high marginal production cost compared to the increase in the recovery rate that makes the monopolist conservationist on the one side, and the generic industry disciplined on the other. In the real world, one may conjecture that the R&D costs are most important and that the marginal production cost is relatively low in the pharmaceutical industry.

2.4 Conclusion

This paper has focused on the pricing of an antibiotic drug by a farsighted producer whose monopoly power is protected by a patent, in the context where the efficacy of the antibiotic (its quality) and the overall level of infection (the market size) are endogenously determined by antibiotic sales over time. We show that the bio-economic system is characterized by a turnpike property. This means that price will move towards the steady-state price level that would be charged by an infinitely-lived monopolist and will remain in the neighborhood of that price for a period of time. The period of time in question will depend on the length of the patent life. Towards the end of the patent protection, the monopolist will begin acting more and more myopically, leading to a continuous decrease in price. When the patent expires, a discontinuous fall in price occurs as the generic industry takes over. We argue that, for reasonable bio-economic parameters of the model, the steady state which is targeted by the monopolist brings two effects into balance: the fitness cost effect (benefiting antibiotic efficacy) and the natural selection effect (favoring a dominance of the drug-resistant version of the bacterial population). Thus, antibiotic efficacy will generally find itself somewhere between its upper and lower bound over a period of time. In that case, it will, in the end, start decreasing, as will the level of infection, reflecting the fact that the monopolist attaches less and less value to the quality and the market size of the antibiotic as the patent nears expiration.

It should be pointed out that those results are obtained under some assumptions concerning the strategies available to the monopolist once the patent expires. For instance, the monopolist may have the possibility of practicing price discrimination for a while, by selling the brand name at a high price, and selling his own generic version before the patent has expired. This might lead to a Stackelberg-type market structure during the generic phase of the industry. Another possibility that has not been taken into account is that the monopolist may attempt to "improve" the biological formula of the drug slightly, at a cost, in the hope of getting a new patent protection. Taking those additional possibilities into account would of course have an impact on the price path during the period of patent protection, but would not necessarily alter the underlying turnpike property described here. How exactly the price path would be affected is however a matter for further research. Another important avenue for further research would consist in endogenizing R&D expenditures, which have been treated as a sunk cost here, and considering the socially optimal patent protection in a context where bacterial resistance to the drug is a significant issue.

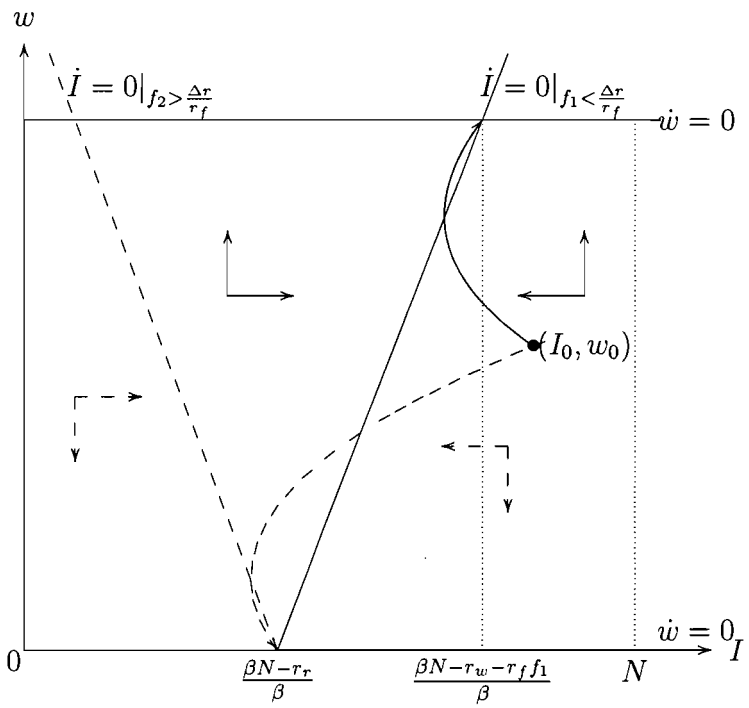

Figure 2.1: The phase diagram

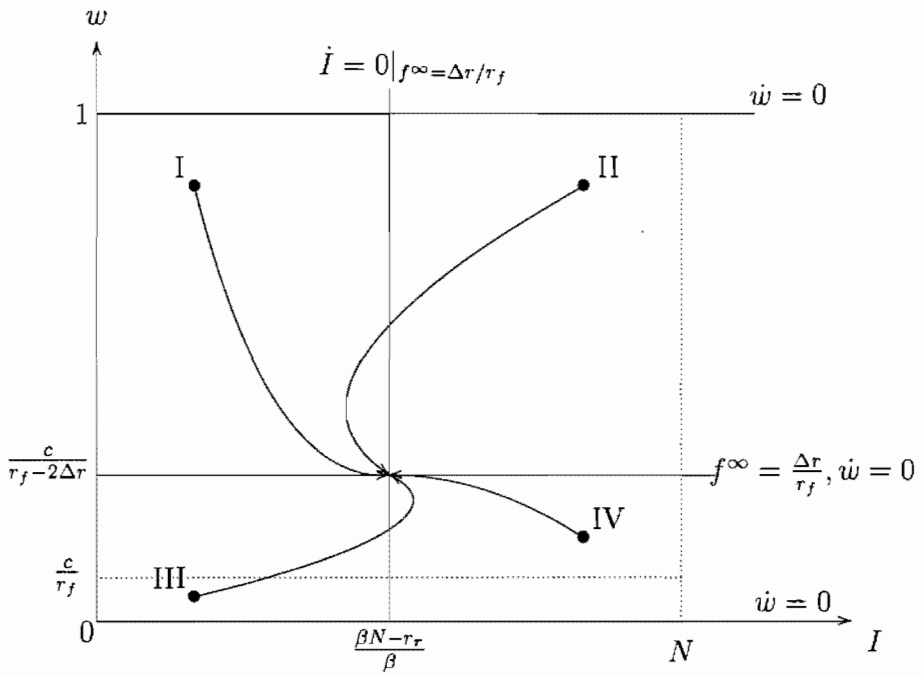

Figure 2.2: Convergence to steady state under the myopic monopolistic programme

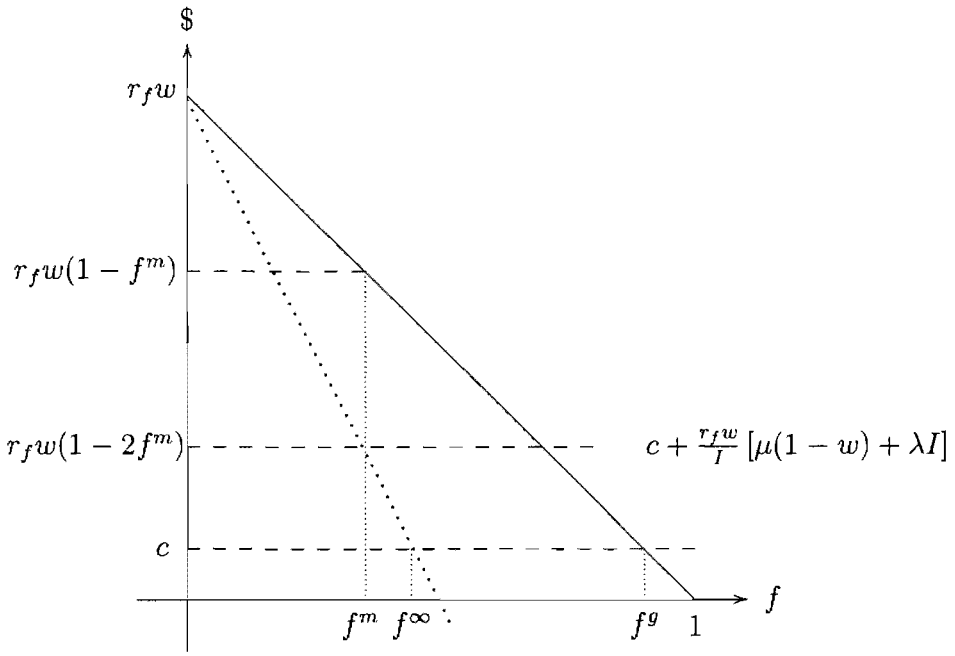

Figure 2.3: Monopolistic interior solution f^m at state (w, I) at time t

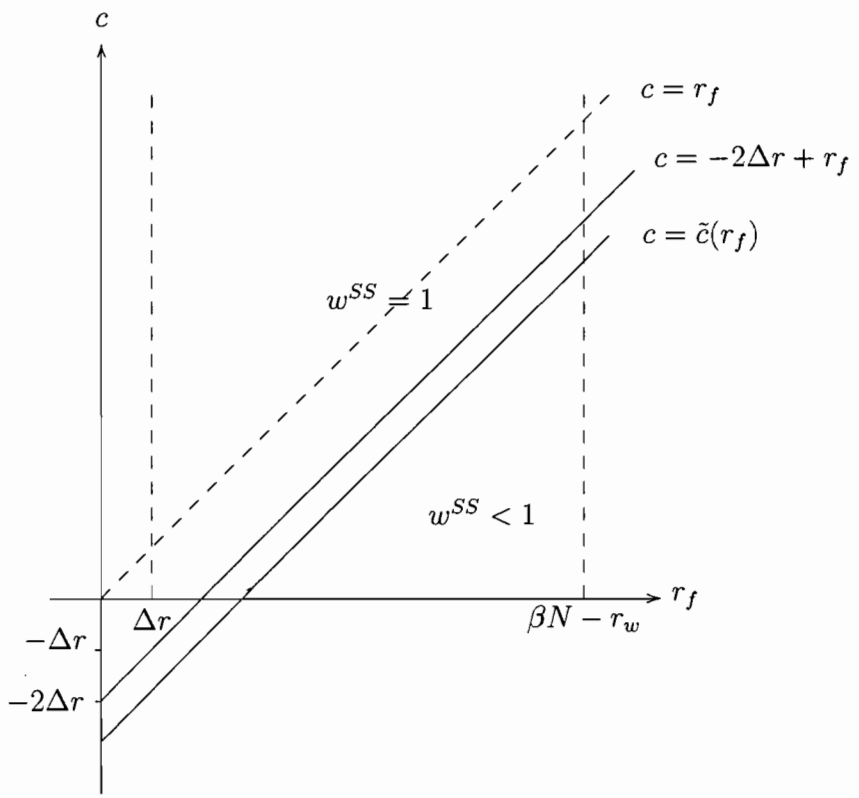

Figure 2.4: Steady-state configurations

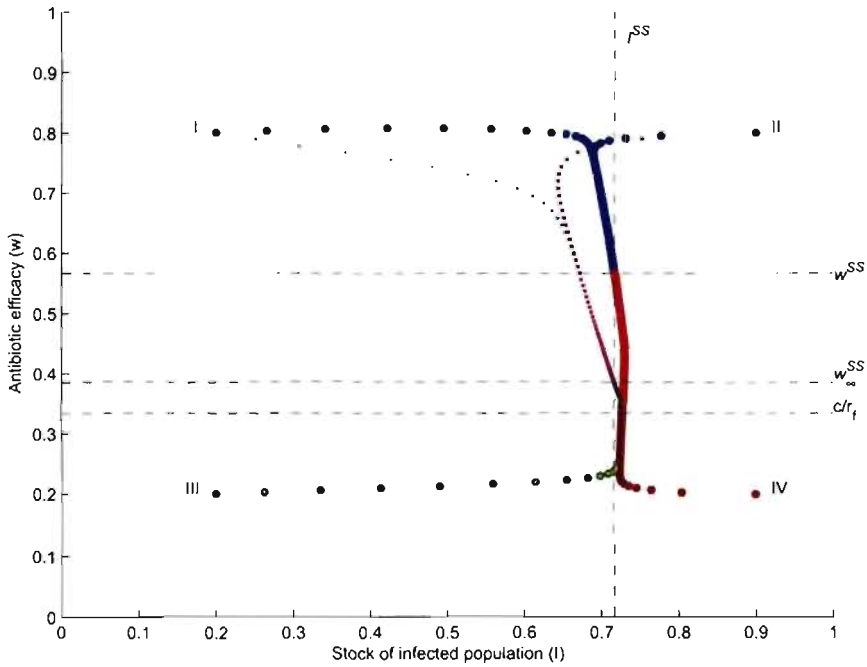

Figure 2.5: Convergence to interior steady state

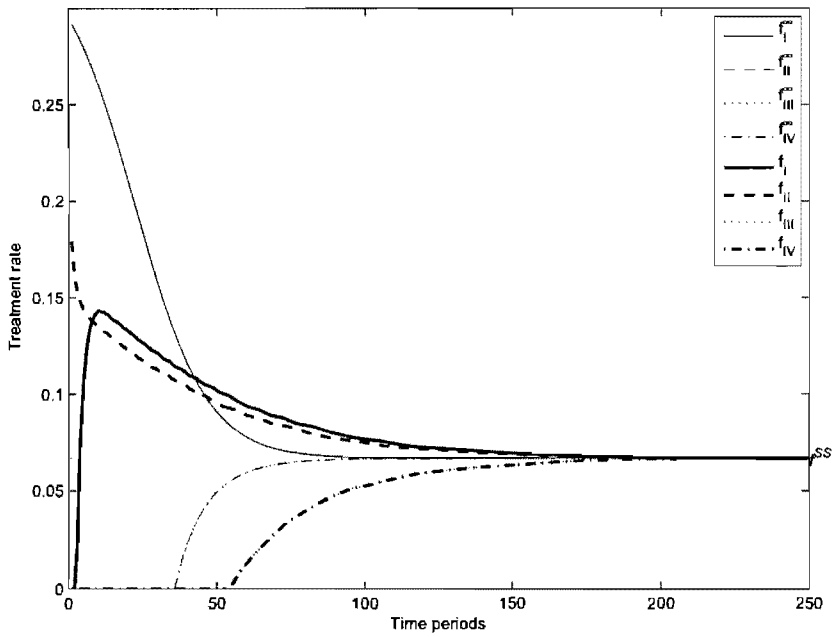

Figure 2.6: Treatment rates converging to $f^{SS} = \frac{\Delta r}{r_f}$

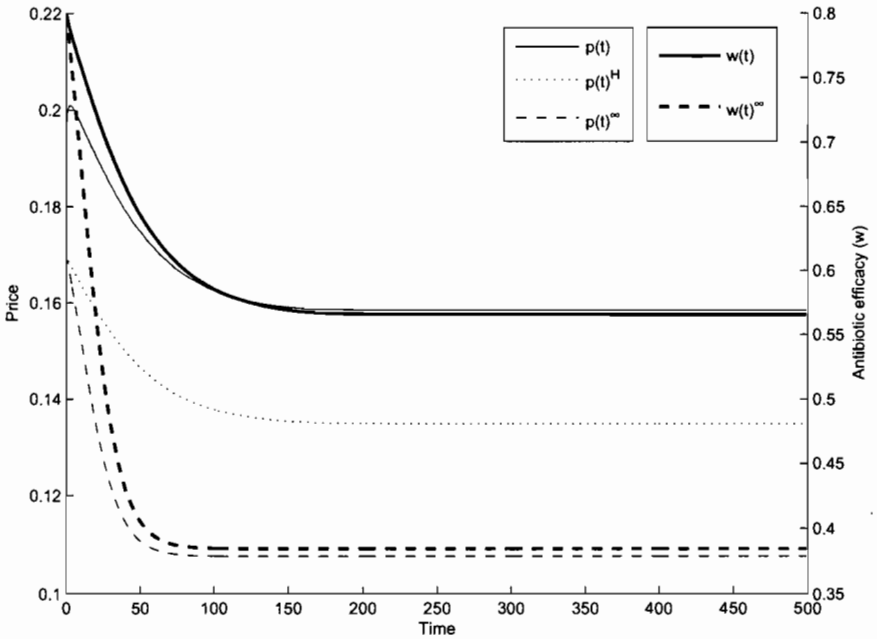

Figure 2.7: Price paths departing from initial state of type II

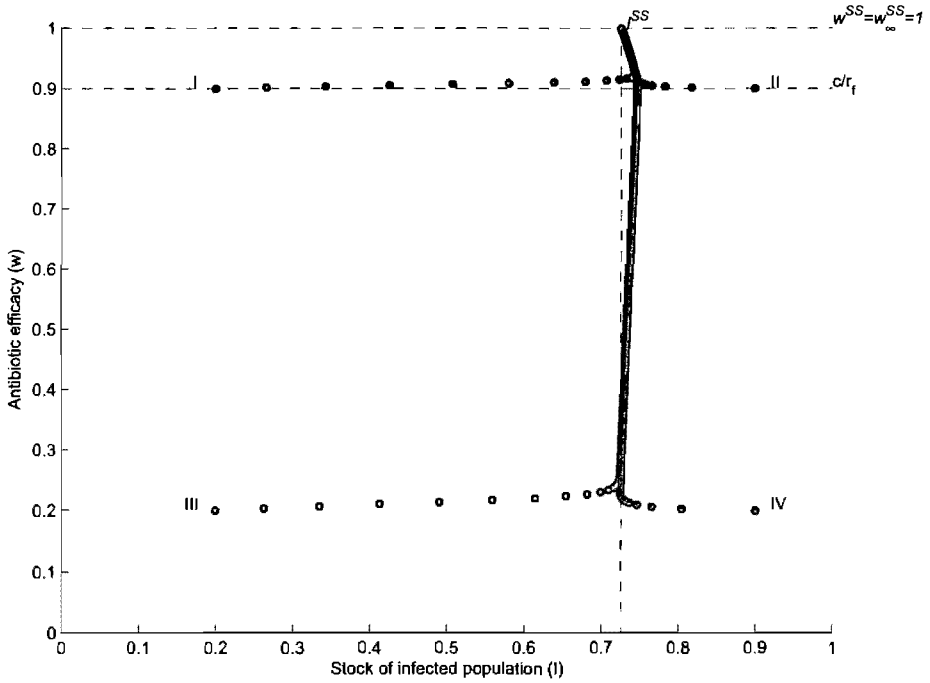

Figure 2.8: Convergence to steady state with $w^{SS} = 1$

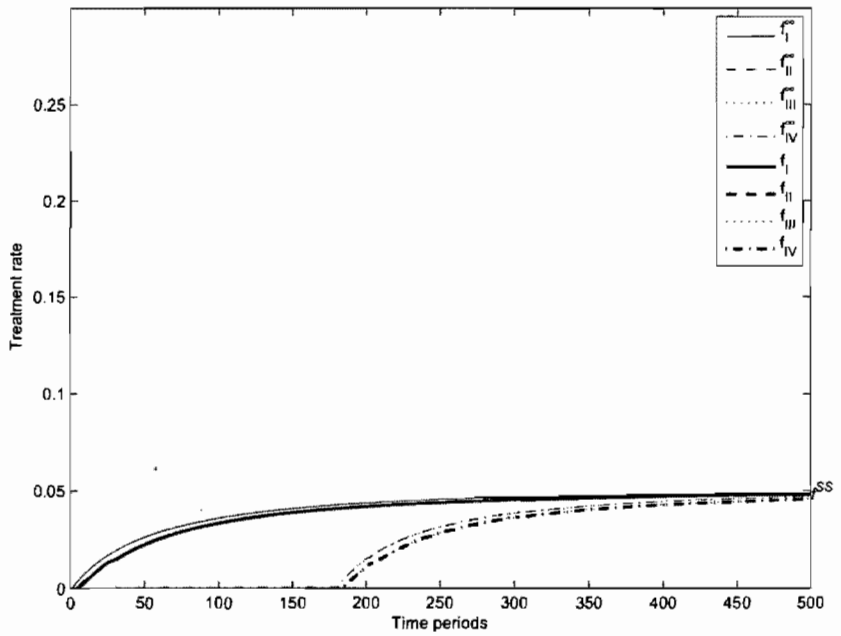

Figure 2.9: Treatment rates converging to steady state with $w^{SS} = 1$

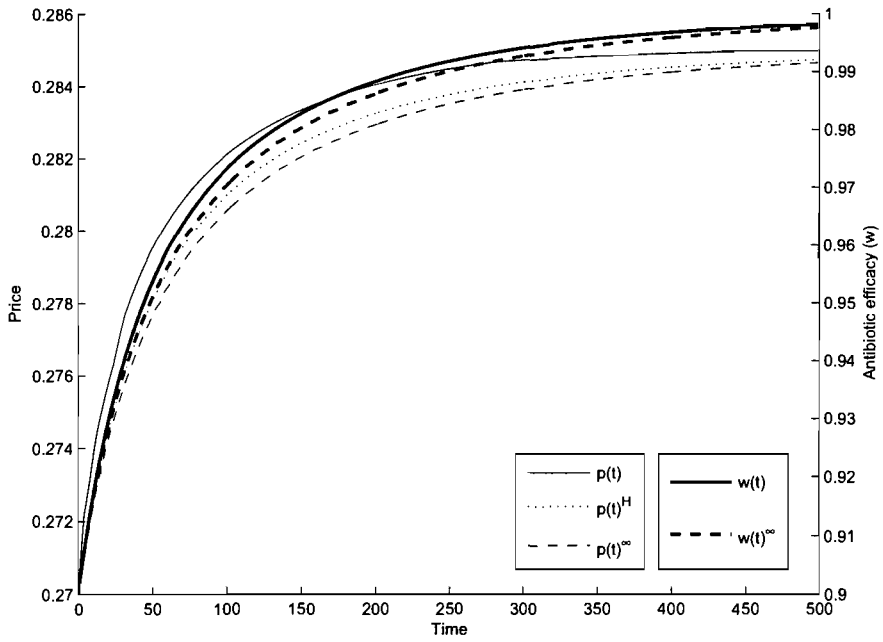

Figure 2.10: Price paths departing from initial state of type II

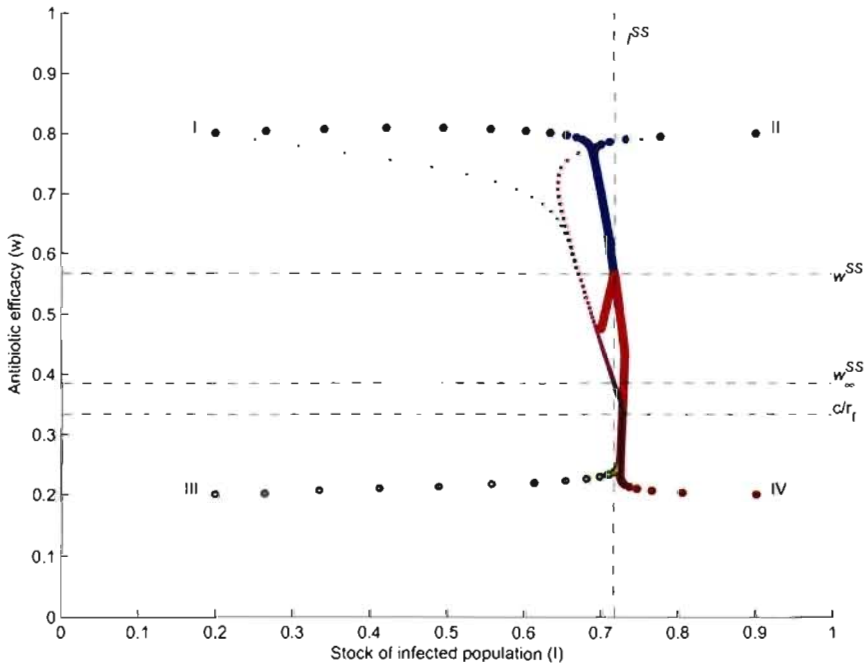

Figure 2.11: Evolution of state variables (I, w) and the turnpike

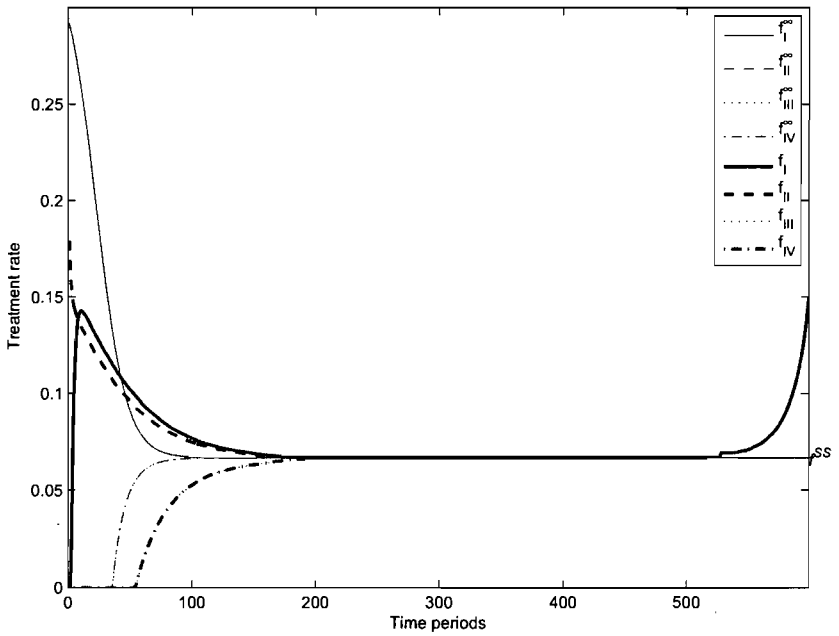

Figure 2.12: Evolution of treatment rate f and the turnpike

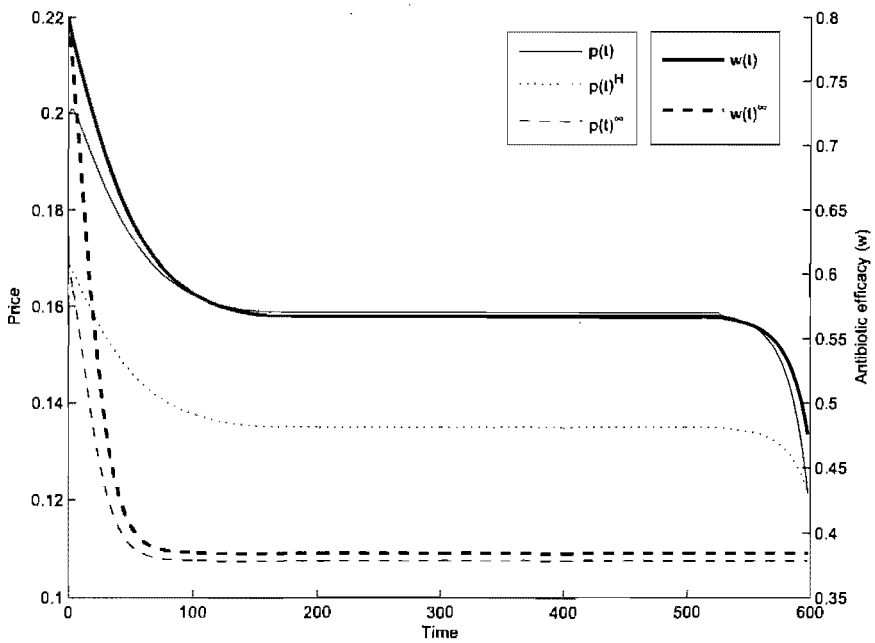

Figure 2.13: Price paths departing from initial state of type II and the turnpike

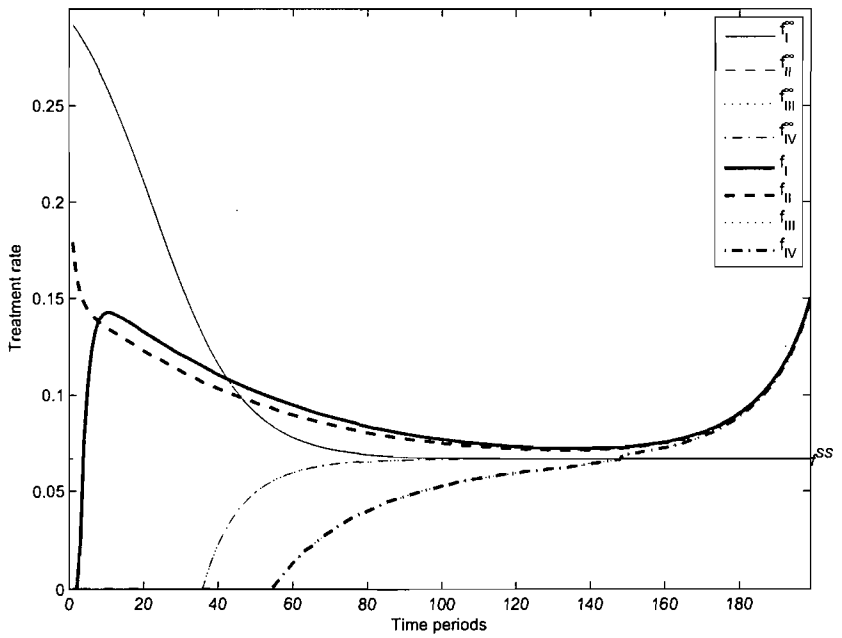

Figure 2.14: Evolution of treatment rate f with approximate turnpike

CHAPITRE 3

OPTIMAL REFUGE STRATEGIES TO FIGHT PEST RESISTANCE TO GM CROPS

3.1 Introduction

Genetically modified (GM) crops have been introduced in the commercial agriculture, notably in the US and Canada to prevent severe loss due to pest invasions. A prominent example is that of *Bt*-corn which can resist the European corn borer.[1] However, concern with the potential rise of *Bt*-resistant pest populations in the future has led to the introduction of mandatory refuge areas by the US Environmental Protection Agency (EPA), and thus limits the use farmers can made of *Bt*-corn.

In the absence of a refuge zone, natural selection of the *Bt*-resistant pest population occurs. This is because the *Bt*-susceptible pests are unable to feed on GM corn and die, so that their genetic information will not be able to spread within the pest population over time. By introducing a refuge area in which regular corn is planted in the neighborhood of the *Bt*-corn, the selective pressure put on the susceptible pests is reduced and, by this, the genetic pool can possibly preserve its susceptibility to *Bt*-corn. The size of the refuge area thus provides a tool to manage pest resistance.

The EPA policy gave rise to some contributions in the fields of natural resource and agricultural economics that try to assess the impact of the refuge on the pest population and the damage caused to production. Some research work also questions the design of the pest resistance strategy (size of the refuge, location, alternative regulation to manage pest resistance).[2] Most of the papers rely on simulations using a combined biological and economic model. For instance, Hurley *et al.* (2001) provide an assessment of pest resistance and population dynamics,

[1]This type of GM corn expresses the microorganism *Bacillus thuringiensis* into the corn genome. By this it becomes poisonous to the pest.

[2]See for instance Bourguet *et al.* (2005) and Vacher *et al.* (2006).

as well as the farmer's profits, based on real-world estimated parameters within an exogenously given finite time horizon. Laxminarayan and Simpson (2002) complement this approach with some analytical results. They explicitly derive the optimality conditions for the refuge area in a stylized dynamic model adapted from epidemiology. Their dynamic control problem is rather complex, due to the coexistence of two dynamic equations that constrain the objective of minimization of the damage caused to the crop. Laxminarayan and Simpson manage to solve it by focusing on a particular steady state in which pest resistance is neither eradicated nor dominates the whole population. At this particular steady state, the effect of an increase in resistance due to the use of the *Bt*-crop is compensated by the effect of a (higher) fitness cost incurred by resistant pests.[3]

The objective of this paper is to provide a broader analysis of the dynamic of pest resistance and its management strategy, particularly when out of the steady state. We deal with a dynamic biological model which takes into account both the gene frequency and the pest population.[4] It is combined with an economic objective: to maximize profits or, equivalently, to minimize costs caused by the pest attack and the use of GM corn.

The paper is structured as follows. In section 3.2, we present the bio-economic model. We investigate the evolution and the long-run steady states of the biological system. We show that Laxminarayan and Simpson's steady state is quite restrictive. It is one of three possible steady states, the other two being characterized by either the eradication or the full spread of the resistance gene. In section 3.3, we address the size of the socially optimal time-invariant refuge zone. Several simulations are presented which point out the richness of the dynamic paths.

[3]This steady state can be maintained by a refuge zone, the size of which lies strictly between 0% and 100% of the overall cultivated surface. However, since their objective function is linear in the refuge zone (the control variable of the dynamic problem), attention should be paid to the lower and upper bound of 0% and 100%, since the optimal solution will generally be characterized by the bang-bang property, possibly combined with a singular solution.

[4]The entomological model we present here is a continuous time version of Hurley *et al.* (2001) with one generation of pests per season. We believe that it has greater validity than that proposed by Laxminarayan and Simpson (2002) as it is derived from a population growth model, were the overall growth rate of the population is determined by the average genetic fitness of the population.

Slight variations of parameters may lead to a different steady-state. Among the key parameters are the discount rate, the supplementary cost of the *Bt*-corn and the fitness cost of the resistant pests. In section 3.4, we state the optimal control problem, and show that the optimal solution of the refuge size is of the bang-bang type and involves a singular control. A sensitivity analysis with respect to the bio-economic parameters indicates for which values of the gene frequency and the pest population a singular solution is mandated. We conclude in section 3.5.

3.2 The model

The model is made up of a set of constraints coming from the biological literature to which is added an economic objective function. We first turn to a description of the biological model.

3.2.1 Biological foundations

The biological dynamics are based on the Fisher-Haldane-Wright model, which analyzes the evolution of a population's genetic diversity and its population size over time.[5] In the particular case under consideration here, we refer to a population of insects which, depending on their genetic information, may be resistant or susceptible to GM organisms like *Bt*-corn. Each insect inherits the information for being resistant or susceptible from its parents. In biological terms, we assume a genetic system of one locus with two alleles.[6] We consider a deterministic environment in which natural selection drives the evolution of the population and its genetic composition over time.

Omitting the time indices, we let p_r (respectively p_s) represent the fraction of

[5] See for instance Roughgarden (1998), chapter 5.

[6] As stated in Roughgarden (1998), "[F]or our purposes, a "locus" is a spot on a chromosome. Two different genes that can occupy the same spot are called "alleles". Typically, an organism has one chromosome from its father and a matching chromosome from its mother. Therefore, it has two alleles at each locus, and the pair of alleles at a locus is called its "genotype" at that locus. [...] If both organism's alleles at a locus are the same it is called a "homozygote", otherwise it is called a "heterozygote". (p.152)

alleles in the system that are resistant (respectively susceptible) to Bt-corn at time t. At any time t, we have $p_r + p_s = 1$. These alleles stem either from the resistant or susceptible homozygotic, rr, ss, and heterozygotic genotypes rs or sr. Assuming random mating, the frequency of resistant genotype rr is p_r^2. The population of pests with genotype ij at time t is denoted N_{ij} for every $i, j = r, s$. The number of alleles i is N_i for $i = r, s$. The overall pest population in the ecosystem is N.

We assume that the population of insects grows logistically. More precisely, following Ginzburg (1983), chapter 2, we model the growth rate of the pest population of genotype i, j as

$$\frac{\dot{N}_{ij}}{N_{ij}} = \epsilon_{ij} - N\gamma, \tag{3.1}$$

where ϵ_{ij} is the intrinsic growth rate (*i.e.* the growth rate in the absence of density dependence) and γ captures the density dependence caused by the pest population competing for resources.

We model $\epsilon_{ij} = gw_{ij}$, in which we separate a genotype-independent birth minus death rate g and the genotype-dependent survival rate on Bt and refuge w_{ij}. Our formulation of the genotype-dependent survival rates is a particular case of the ones proposed in Lenormand and Raymond (1998), Bourguet *et al.* (2000), and Vacher *et al.* (2005). Pests with genotypes rs, sr and ss die on the Bt-field but survive on the refuge area. We refer to them as susceptible pests. Formally, their genotype-dependent survival rate is 0 on Bt-corn and 1 on the refuge. Given a refuge of size q, their average genotype-dependent survival rate is $w_{rs} = w_{sr} = w_{ss} = q \times 1 + (1 - q) \times 0 = q$. Pests with genotype rr survive on both, Bt and refuge areas, but face a fitness cost of resistance c irrespectively of the corn variety on which they feed. Their genotype-dependent survival rate is thus $w_{rr} = 1 - c$ in Bt and refuge areas. We refer to them as resistant pests.[7]

[7]Lenormand and Raymond (1998) and Vacher *et al.* (2005) include cases with a fitness cost of resistance for heterozygotes and with partial survival of susceptible pests on Bt. For simplicity matters, we abstract from such cases.

The average genotype-dependent survival rate of the allele r is

$$w_r = p_r(1 - c) + (1 - p_r)q. \tag{3.2}$$

This is because the allele r might be associated with an allele r (which happens with probability p_r in average) to form the genotype rr or to s (which happens with probability $p_s = 1 - p_r$) to form the genotype rs or sr. The growth rate of allele r is

$$\frac{\dot{N}_r}{N_r} = gw_r - N\gamma, \tag{3.3}$$

with w_r defined in (3.2). Lastly, the overall genotype-dependent survival rate is

$$\bar{w} = (1 - c)p_r^2 + q(2(1 - p_r)p_r + (1 - p_r)^2). \tag{3.4}$$

It weights the survival rate $1 - c$ of genotype rr by its frequency in the pest population, p_r^2, and the average survival rate q of the susceptible genotypes rs, sr and ss, with their respective frequencies $p_r(1 - p_r)$, $(1 - p_r)p_r$ and $(1 - p_r)^2$. The growth of the population is

$$\frac{\dot{N}}{N} = g\bar{w} - N\gamma, \tag{3.5}$$

with $\bar{w}$ defined in (3.4).

We now derive the dynamic of alleles r. Since each pest has two alleles, N pests yield $2N$ alleles. Since the alleles r are in proportion p_r in the $2N$ alleles, the number N_r of alleles r in the pest population is

$$N_r = p_r 2N. \tag{3.6}$$

Differentiate (3.6) with respect to time yields

$$\frac{\dot{p}_r}{p_r} = \frac{\dot{N}_r}{N_r} - \frac{\dot{N}}{N}. \tag{3.7}$$

Combining the last equality with (3.2) – (3.5) yields the following laws of motion:

$$\dot{p}_r = p_r^2(1-p_r)g(1-c-q) \tag{3.8}$$

$$\dot{N} = Ng\left(p_r^2(1-c-q)+q\right) - \gamma N^2 \tag{3.9}$$

The above two equations summarize the dynamic of the biological model. They link the variation of two state variables of interest, namely pest resistance as measured by the frequency of the resistance allele in the gene pool p_r, and the pest population N, with the endogenous control variable $q \in [0,1]$ which is the percentage of refuge area. The variation of the two state variables depends on three exogenous parameters: the genotype-independent growth rate of the population g, the fitness cost of the GM resistent pests c and the intraspecific competition within the pest population captured by γ. They are all strictly positive and $c < 1$.

Consider equation (3.8). The susceptibility of the gene pool, measured by $p_s = 1 - p_r$, is the "mirror image" of its resistance and can be understood as a renewable resource. Without a refuge ($q = 0$ for all t), the level of pest resistance p_r will necessarily increase up to its upper bound of 1, since then $\dot{p}_r > 0$. At the same time, pest susceptibility, p_s, decreases until exhaustion ($p_s = 0$). Conversely, without GM seed ($q = 1$ for all t), $\dot{p}_r < 0$ because of the higher fitness cost of resistant pests. Pest resistance in the gene pool decreases down to $p_r = 0$ and, therefore, the resistant gene is eradicated. As a consequence, susceptibility grows up to fill all the gene pool.

3.2.2 Dynamic of the biological model

Before introducing the economic assumptions, we examine of the dynamic of the biological model summarized by the two differential equations (3.8) and (3.9).

Consider first the evolution of genetic resistance (3.8). It is kept constant when $q = 1 - c$ (*i.e.* when the size of the refuge exactly matches the fitness cost). For a greater refuge size, pest resistance decreases, while it increases for a smaller refuge. As expected, the refuge might contain or even reduce pest resistance over time due

to the fitness cost c.[8]

The second equation (3.9) can be rewritten as a logistic function which is standard in the renewable natural resource literature:

$$\frac{\dot{N}}{N} = G(p_r, q)\left(1 - \frac{N}{K(p_r, q)}\right)$$

with

$$\begin{aligned} G(p_r, q) &= p_r^2 g(1 - c - q) + gq \\ K(p_r, q) &= \frac{G(p_r, q)}{\gamma} \end{aligned} \tag{3.10}$$

where $G(p_r, q)$ is the overall population growth rate, and $K(p_r, q)$ is the carrying capacity, which are both endogenously determined as a function of the fraction of resistant alleles, p_r, as well as the refuge size q. In contrast with the logistic functions commonly used in natural resource economics, both $G(p_r, q)$ and $K(p_r, q)$ depend on the pest gene pool p_r, which varies over time, and the refuge strategy q, which may vary over time.

We now describe the steady states of the dynamic biological system defined by (3.8) and (3.9). Setting $\dot{p}_r = \dot{N} = 0$ defines the following three steady states:

$$S0 \equiv (N^{S0}, p_r^{S0}) = \left(\frac{gq}{\gamma}, 0\right), \tag{3.11}$$

$$\text{and} \quad S1 \equiv (N^{S1}, p_r^{S1}) = \left(\frac{g(1-c)}{\gamma}, 1\right). \tag{3.12}$$

$$Si \equiv (N^{Si}, p_r^{Si}) = \left(\frac{g(1-c)}{\gamma}, p_r \in [0, 1]\right). \tag{3.13}$$

A quick examination of the dynamic system allows us to describe the convergence process to steady states for a refuge which is constant over time, $\bar{q}$. If $\bar{q} > 1 - c$ (constant high refuge area), and therefore $\dot{p}_r < 0$ for any value of p_r, the resistance allele frequency decreases and therefore tends toward its lower bound $p_r^{S0} = 0$ and

[8] See for instance Tabashnik and Carrière (2004) and the references cited therein.

the steady state $S0$. Resistance converges to eradication and the pest population reaches the steady-state level $N^{S0} = g\bar{q}/\gamma$. If $\bar{q} < 1 - c$ (constant low refuge area), and therefore $\dot{p}_r > 0$, the resistance allele frequency increases and therefore tends toward its upper bound $p_r^{S1} = 1$, that is steady state $S1$. The resistance genotype spreads out to the whole pest population which converges to a steady-state pest population $N^{S1} = g(1-c)/\gamma$. It is lower than the steady-state pest population if resistance tends to be eradicated (N^{S0}) thanks to the fitness cost c. Lastly, if $\bar{q} = 1 - c$, *i.e.* the percentage of refuge exactly matches to resistance fitness cost c, then $\dot{p}_r = 0$ for any value of p_r. Resistance is contained at the level p_r which defines a set of interior steady states Si. The pest population converges towards $N^{Si} = g(1-c)/\gamma = N^{S1}$.

To analyze in more detail the dynamic of the biological system, in particular the simultaneous motion of both state varaibles p_r and N, we draw a phase diagram in the $(N \times p_r)$ space in Figure 3.1 below. The isoclines for p_r and N are the geometric loci where $\dot{p}_r = \dot{N} = 0$. We also represent by arrows the dynamic forces driving the system when out of the isoclines. Three different regimes must be distinguished depending on whether $q \gtreqless 1-c$. Setting $\dot{p}_r = 0$ in equation (3.8) yields the isoclines $p_r = 0$ and $p_r = 1$ for the resistant allelic frequency, on which lie the corner steady states $S0$ and $S1$ respectively. If the refuge area takes the critical value $q = 1 - c$, the $\dot{p}_r = 0$ isocline is horizontal at some level strictly between 0 and 1 (not shown in Figure 3.1). Setting $\dot{N} = 0$ in equation (3.9), yields the $\dot{N} = 0$ isocline as a function of p_r:

$$N(p_r) = \frac{g[p_r^2(1-c-q)+q]}{\gamma}. \tag{3.14}$$

It is concave (convex) in p_r whenever q is greater (smaller) than $1-c$. In the special case when $q = 1 - c$, which allows to keep the level of pest resistance p_r constant, the $\dot{N} = 0$ isocline is a vertical line passing through $N = g(1-c)/\gamma$ (not shown in Figure 3.1).[9]

[9]The forces driving the pest population N when out of the N-isocline are derived by calculating the derivative $\partial N(p_r)/\partial p_r = 2gp_r(1-c-q)/\gamma \gtreqless 0$ for $q < 1 - c$. Thus for values of p_r above the $\dot{N} = 0$ isocline, N must increase. The converse is true for a value of p_r below the N-isocline,

We are now able to address the simultaneous behavior of the two state variables p_r and N of the biological system for a constant refuge $q(t) = \bar{q}$ starting from the initial state (N_0, p_{r0}) represented in Figure 3.1. For $\bar{q} < 1 - c$, the driving dynamic forces are represented in Figure 3.1 by the dashed arrows and the dashed line $\dot{N} = 0$ (the plain line $\dot{N} = 0$ does not apply). Since the refuge area is small, pest resistance monotonously increases over time (see equation (3.8)). The level of the pest population decreases initially and eventually crosses the $\dot{N} = 0$ isocline. From that point of time, the pest population increases up to its long-run steady-state value. The arc of arrows shows the qualitative evolution of the state variables over time from the interior initial state to the steady state $S1$, at which Bt-corn has lost all its efficacy ($p_r = 1$). For $\bar{q} > 1 - c$, the dynamic is represented by the solid arrows and line. A large refuge reduces resistance over time. For the initial state shown, the level of the pest population increases monotonously over time. The dynamic system converges to $S0$. Finally consider the case, when the refuge area takes the critical value $\bar{q} = 1 - c$. The pest resistance $p_r(t)$ remains unchanged and equal to its initial value p_{r0} and the pest population converges to $g(1 - c)/\gamma$, *i.e.* the interior steady state Si is reached.

From this preliminary analysis, we can already posit some principles on the constant refuge as a pest resistance management strategy. First, the extensive use of Bt-corn through a low refuge zone reduces the pest population at a cost of (almost) exhausting susceptibility to Bt in the long run (steady state S1 as defined in (3.12)). Second, the objective of keeping the ecological system (almost) completely free from Bt-resistant genotypes comes at a cost of a higher steady-state level of pests in the long run (steady state as in (3.11) with $q > 1 - c$). Third, the interior steady state (as in (3.13)), in which resistance is neither eradicated nor fully spread in the pest population, but controlled for to be constant, is obtained with a unique constant refuge area. It is the only steady state analyzed by Laxminarayan and Simpson (2002), whereby the over-mortality of susceptible pests is exactly

implying a decreasing level of the pest population.

compensated by the fitness cost of resistant pests.

3.2.3 Economic Objective

The economic objective is to maximize the total discounted costs of producing one unit of corn. It is computed as follows. Let Y be the pest-free corn yield at instant t in tons per hectare. It can be reduced due to pest attack. Assume that the loss in corn yield due to one pest per plant is $d\%$ with $1 > d > 0$. The yield from the fraction q of one hectare planted with conventional corn (the refuge) is $Y(1 - dN)$. On the $1 - q$ fraction of Bt-corn, only the fraction p_r^2 of pests with resistant genotypes damage production, which leads to a yield $Y(1 - p_r^2 dN)$. The production of one hectare with a refuge area q is thus $Y[1 - (q + (1 - q)p_r^2)dN]$.

Denote $c_1 > 0$ the additional cost of planting Bt-corn instead conventional, mostly due to more expensive seeds.[10] Let p_Y be the price of a ton of corn. The profit of one hectare of corn with refuge q net of (conventional corn) production costs is:

$$\Pi = p_Y Y \left[1 - (q + (1 - q)p_r^2)dN\right] - (1 - q)c_1 \tag{3.15}$$

From (3.15) we compute the total cost due to pest damages with a refuge q:

$$C(q, p_r, N) = dp_Y Y[(1 - q)p_r^2 + q]N + (1 - q)c_1. \tag{3.16}$$

Divide (3.16) through by $p_Y Y$ to get the relative cost due to pests

$$\tilde{C}(q, p_r, N) = d[(1 - q)p_r^2 + q]N + (1 - q)\tilde{c}_1 \tag{3.17}$$

where $\tilde{c}_1 = c_1/(p_Y Y)$ is the Bt-cost per crop value if no pest damage occurs. The first right-hand term in (3.16) represents the cost associated to pest attack. It is increasing in the refuge area q in the short run as long as $p_r < 1$, *i.e.* there are some

[10] Hurley *et al.* (2001) mention that a supplemental cost of Bt-corn may result from higher quality control costs of the Bt-seed.

susceptible genotypes. However, in the long run, pest resistance p_r may increase, implying rising costs caused by pests. The current refuge q also affects the future pest population N which, in turn, affects future cost C and, therefore, $\tilde{C}$. Hence there is a clear inter-temporal tradeoff between the short and long term impact of the refuge zone q on the farmer's cost. The second right-hand term captures the additional price of the *Bt*-technology.

The economic objective is to minimize the discounted instantaneous relative costs $\tilde{C}$ with respect to q:

$$V(p_{r0}, N_0) = \min_q \int_0^\infty e^{-\rho t} \tilde{C}(q, p_r, N) dt, \tag{3.18}$$

where $\tilde{C}(q, p_r, N)$ is defined in (3.17), subject to the laws of motion of the state variables p_r, and N, as defined in (3.8) and (3.9) and the control constraint $0 \leq q \leq 1$.

3.2.4 Model calibration

We have calibrated the parameters of our model on the basis of several studies related to the subject of *Bt*-resistance. Unless specified differently, Table 3.1 summarizes the parameter values used in the simulations presented later in this paper.

Parameter		Value
N_0	initial average pest population per plant	1.5
p_{r0}	initial resistance allele frequency	0.05
c	fitness cost	0.05
g	growth rate	0.94
γ	intraspecific competition	0.625
d	damage rate	0.043
$\tilde{c}_1$	additional cost of *Bt*-seed	0.03
ρ	discount rate	0.04

Tableau 3.1: Parameter values

Due to the lack of confirmed cases of resistance of the European corn borer to *Bt*-toxins, resistance genetic parameters are unknown. As in Vacher *et al.* (2005), we assume a fitness cost of 0.05 in the benchmark simulation. We assume an initial resistant allelic frequency of $p_{r0} = 0.05$. The initial level of the pest population is assumed to be at its carrying capacity $K(p_r, q)$ defined in (3.10), with $q = 1$, *i.e.* no use is made of *Bt*-seed initially. In that case, we have $K(0.05, 1) = 1.5$. To compare our benchmark simulation results with Hurley *et al.* (2001), we approximate g and γ from their model of two pest generations per season to our model of one pest generation per season as explained in Appendix III.2. We assume an initial 6.4% reduction in grain yield on corn per season (Calvin 1995). Given our initial number of 1.5 pests per plant, we obtain a constant marginal yield loss per pest per plant of $d = 6.4\%/1.5 = 4.3\%$. The ratio $\tilde{c}_1$ is the additional cost of *Bt*-seed of 10$/acre, reported in Onstad and Guse (1999), divided by the value of the crop without damage of 305$/acre in Hurley *et al.* (2001).

3.3 Time-invariant refuge zone

We first analyze the constant refuge zone which is the pest resistance management strategy mandated by the U.S. Environmental Protection Agency. It is appealing due to its simple nature, but it is unlikely to be optimal in our context: an optimal refuge strategy will generally change over time and adjust to the state of the dynamic system. The optimal time-variant strategy will be considered in Section 3.4.

The time-invariant refuge $\bar{q}$ minimizes discounted costs subject to the dynamic constraints of the model. Formally, it solves program (3.18) with the additional constraint $q(t) = \bar{q}$ held constant over time t.

3.3.1 Benchmark analysis

Before addressing the socially optimal time-invariant refuge zone, we present a benchmark analysis for the cases where a constant refuge zone $\bar{q}$ takes the value 0

Refuge ($\bar{q}$)	Discounted Costs
0	0.7856
1	1.6566
$1-c$	1.5457

Tableau 3.2: Benchmark costs

(no refuge), 1 (no use of Bt-seed) and 1-c (control of pest resistance). Figure 3.2 shows the evolution of the state variables (N, p_r) over time for each benchmark.

Consider first the case of a refuge set to zero. This leads to a sharp decrease in the level of the pest population initially, combined with a relatively small increase in the level of the resistant allelic fraction. The increase in the level of the resistant allelic fraction becomes eventually more pronounced and, as the pest population becomes more resistant, the Bt-plantings lose their efficacy, so that pest population increases. The system converges to the steady state $S1$ in which the overall pest population becomes resistant towards the Bt-seed but the steady-state level of the pest population is relatively low (see (3.12)). Consider now the option of not using Bt-seed, formally $\bar{q} = 1$. The system converges to the steady state $S0$ as defined in (3.11). Resistance decreases monotonously and is eradicated in steady state, while the level of the pest population increases slightly (admittedly difficult to see from the Figure 3.2) and reaches its steady state, with a higher level than in $S1$. Finally, consider the case where $\bar{q} = 1 - c$ over time. As can be seen from equation (3.8), the level of resistance remains constant, and the pest population decreases to its steady-state. The steady state is of the type Si as defined in (3.13).

The evolution of the discounted costs associated to the state dynamics just presented, is shown in Figure 3.3. The overall discounted costs are summarized in Table 3.2. The lowest costs are associated to the case where no refuge is planted. Using only Bt-seed over time leads, as described earlier, to a sharp decrease in the number of pests per plant, thus limiting considerably the damage caused to the crop initially. The negative effect of rising resistance, combined to a rising pest

population occurs in later periods only. This can be seen in Figure 3.3. Though discounted costs eventually lie above the costs associated to the other two benchmark scenarios, the low discounted costs that occur initially in the case of zero refuge dominate.

3.3.2 Sensitivity analysis

In what follows we present a sensitivity analysis on how the fitness cost of the resistant pest population (c), the additional cost of Bt-seed ($\tilde{c}_1$), as well as the discount rate (ρ) affect the constrained time-invariant refuge zone ($\bar{q}$). In Table 3.3, we represent the time-invariant cost minimizing refuge zone $\bar{q}$ and the associated cost determined by the integral $V(p_{r0}, N_0)$ defined in (3.18) for a variation of the fitness cost c. As the fitness cost increases, the time-invariant refuge decreases, as does the discounted cost associated to pest damage and Bt-expenses. For all parameter configurations, we have $\bar{q} < 1 - c$, so that it is optimal to tend towards the steady state $S1$, in which allelic resistance is at its maximum level. For higher values of the fitness cost, the steady-state level of the overall pest population will be lower, implying lower costs in the future.

c	0	0.05	0.10	0.20	0.35	0.55
$\bar{q}$	0.192	0.187	0.183	0.177	0.172	0.170
$V(.)$	0.7506	0.7480	0.7458	0.7431	0.7413	0.7407

Tableau 3.3: Variation of fitness cost (c)

$\tilde{c}_1$	0	0.03	0.06	0.10	0.1136	0.116	0.120
$\bar{q}$	0	0.187	0.477	0.832	0.950	0.970	1
$V(.)$	0.018	0.7480	1.2602	1.615	1.652	1.655	1.657

Tableau 3.4: Variation of supplemental cost ($\tilde{c}_1$)

The sensitivity analysis with respect to the supplemental cost of Bt-seed is summarized in Table 3.4. It indicates that the refuge area is increasing in the supplemental cost. The parameter configuration considered here shows that for a large range of $\tilde{c}_1 < 0.1136$, the refuge area is such that $\bar{q} < 1 - c$, implying that the system tends to the steady state characterized by the maximum level of resistance $S1$. For $\tilde{c}_1 = 0.1136$, the system tends to the steady state Si, at which the level of susceptibility of the pest population is a renewable resource. For higher values of $\tilde{c}_1$, the system tends to the steady state $S0$ in which resistance is eradicated. The refuge zone reaches its upper bound for $\tilde{c}_1 \geq 0.12$.

ρ	0	0.02	0.04	0.06	0.1	0.12
$\bar{q}$	0.939	0.309	0.188	0.134	0.047	0.00
$V(.)$	∞	1.550	0.748	0.511	0.319	0.270

Tableau 3.5: Variation of discount rate (ρ)

In Table 3.5, we show the results of the sensitivity analysis with respect to the discount rate. It reveals that the time-invariant refuge area ($\bar{q}$) is decreasing in the level of the discount rate (ρ). As less weight is attached to costs in future periods for higher discount rates, the regulator cares less about future levels of resistance, implying a lower value of refuge to be optimal. For a positive discount rate, it is optimal to have $\bar{q} < 1 - c$, so that the dynamic system tends to the steady state $S1$ with the highest resistance level, as defined in (3.12). Minimized discounted costs, $V(.)$, are decreasing in the discount rate. Though lower refuge areas imply higher expenses on Bt-seed over time, as well as higher levels of resistance, the overall discounted sum decreases.[11]

[11]When the discount rate takes the value $\rho = 0$, the inter-temporal cost $V(.)$ goes to infinity. This is because current costs are strictly positive as expenditures on Bt-seeds occur, as well as damage from the pest population, which cannot be eradicated.

3.4 Time variant refuge zone

The time variant refuge zone $q(t)$ minimizes discounted costs subject to the dynamic constraints of the model. Formally, it solves program (3.18).

3.4.1 Analytical analysis

The current value Hamiltonian function associated to the dynamic minimization problem is given by (we omit the time indices):

$$\begin{aligned} H(p_r, N, \mu, \lambda, q) &= -\tilde{C}(p_r, N, q) + \mu p_r^2(1-p_r)g(1-c-q) \\ &\quad +\lambda\left[Ng\left(p_r^2(1-c-q)+q\right) - \gamma N^2\right], \end{aligned} \tag{3.19}$$

where μ and λ represent the shadow values associated to the level of allelic resistance and the pest population respectively. The Hamiltonian function is linear in the control. The partial derivative of the Hamiltonian function with respect to the control variable is:

$$\partial H/\partial q = -d(1-p_r^2)N + \tilde{c}_1 - \mu p_r^2(1-p_r)g + (1-p_r^2)Ng\lambda. \tag{3.20}$$

An optimal solution must satisfy the following necessary conditions:

$$\frac{\partial H}{\partial q}q = 0, \quad \frac{\partial H}{\partial q} \geq 0, \quad q \geq 0, \quad \text{or} \tag{3.21}$$

$$\frac{\partial H}{\partial q}(1-q) = 0, \quad \frac{\partial H}{\partial q} \leq 0, \quad q \leq 1 \tag{3.22}$$

$$\dot{\mu} - \rho\mu = d(1-q)2p_rN - g(1-c-q)p_r[\mu(2-3p_r) + 2\lambda N] \tag{3.23}$$

$$\dot{\lambda} - \rho\lambda = d[(1-q)p_r^2 + q] - \lambda[g(p_r^2(1-c-q)+q) - 2\gamma N] \tag{3.24}$$

If we define the switching function $\Omega(t) \equiv \partial H/\partial q$, the optimal refuge zone can be expressed as

$$q(t) = \begin{cases} 0 & \text{if } \Omega(t) < 0 \\ \hat{q}(t) \in [0,1] & \text{if } \Omega(t) = 0 \\ 1 & \text{if } \Omega(t) > 0 \end{cases} \tag{3.25}$$

where $\hat{q}$ is the singular control that applies whenever the switching function $\Omega(t)$ is zero.

The costate variables μ and λ will be negative. Since only the damage caused by susceptible pests can be controlled at a given point of time by the refuge zone, it is the marginal damage caused by the susceptible pest population, $d(1-p_r^2)N$, that is compared to the full marginal cost of using Bt-seed, $\tilde{c}_1 - \mu p_r^2(1-p_r)g + (1-p_r^2)Ng\lambda$. The shadow values μ and λ being negative, the full marginal cost is decreasing in μ and increasing in λ. Use of the Bt-seed will be made when the marginal damage caused is higher than the full marginal cost related to its use ($\Omega(t) \leqq 0$).

3.4.2 Numerical analysis

In order to characterize the optimal solution and evaluate the social costs associated to the use of Bt-seed, we use numerical simulations.[12] Figure 3.4 displays the optimal control as a function of the state variables. It is generally referred to as the optimal policy function. A projection of Figure 3.4 in the state space (N, p_r) is provided in Figure 3.5. It is divided into two regions of extreme controls, with $q = 0$ and $q = 1$ respectively. If the allelic resistance frequency of the pest population, p_r, is zero, there exists a threshold level for the pest population per plant, N, given by approximately 0.7 pests per plant (on average), for which zero refuge is required (see Figure 3.5). The higher the level of allelic resistance, the

[12]We applied the value function iteration approach to the discrete time analogue of the continuous model, which is presented in Appendix III.1. A detailed discussion of this approach is given in Judd (1998), pp. 412-13. In order to iterate on the value function, the state space is represented by a fine grid of values for the state variables N, and p_r. We have also applied other approaches, notably modified policy function iteration, parametric value function iteration with regression and Chebyshev polynomial interpolation. These approaches were all dominated by the value function iteration on a fine grid. Lenhart and Workman (2007) point out some of the problems arising when dealing numerically with linear control problems.

higher is this threshold level for the pest population. This characterizes the arc at which the step in the policy function from $q = 0$ to $q = 1$ occurs. As can seen from Figures 3.4 and 3.5, a singular control is optimal in the vicinity of the arc.[13]

In our infinite horizon problem, the optimal evolution of the refuge area may be characterized by two different patterns. The first pattern involves a singular control (possibly combined to an extreme control), while the second refers to an alternate extreme control (possibly combined to a singular control). Suppose the initial state (N_0, p_{r0}) lies in the region where $q = 0$ is optimal. The level of the allelic resistance frequency increases inevitably, and eventually reaches the vicinity of the arc, where a singular control applies. Either a singular control is followed forever, converging possibly to $q = 1 - c$, which implies an interior steady state Si with controlled resistance level. Alternatively, the system reaches the region where $q = 1$, which in turn implies a decreasing level of allelic resistance frequency, so that the vicinity of the singular arc is hit again. This movement of switching from one region of an extreme control to another, potentially involving singular controls for some time interval, may continue indefinitely and eventually converges to the vicinity of the interior steady state Si.

In what follows, we present simulation evidence for the dynamics of the control and state variables. The parameters of the model are calibrated as in Table 3.1. Furthermore, we assume $p_{r0} = 0.05$, and the initial number of pests per plant is derived from (3.14) evaluated at $q = 1$, such that $N_0 = 1.5$. The optimal control is characterized by an initially extreme control with $q = 0$, so that only *Bt*-seed is planted (as can be seen from Figure 3.6). This is because the initial value of the resistant allelic fraction is low and *Bt*-plantings allow the level of pests per plant to fall abruptly (as can be seen from Figure 3.7). The control then jumps to the singular control and converges to the interior steady state at which $q^{Si} = 1 - c = 0.95$. The level of the pest population per plant converges to its

[13] Analytically, a singular solution can only occur when the state of the system is exactly on the arc at which $\Omega(t) = 0$. In a numerical approach, we must allow for an approximate, relatively thick, arc.

steady state Si in which the pest population is $N^{Si} = g(1-c)/\gamma = 1.43$. The level of the resistant allelic fraction evolves continuously to its steady state level which is in the proximity of 0.675 as can be seen from Figure 3.8.[14] Figure 3.9 shows the evolution of the state variables in the state space $N \times p_r$. The minimum discounted cost associated to the optimal control computed in this simulation is of 0.7030, and is around 6% lower than the one reported for the constant control $\bar{q}$ for $c = 0.05$ in Table 3.3.

Using the evidence from this simulation in combination with the dynamic forces driving the bio-economic system, we can conjecture the qualitative pattern which the state and control variables will follow. Consider Figure 3.10, in which we have combined the geometric locus where the switching function vanishes, $\Omega(t) = 0$, with the dynamic forces driving the system when $q(t) < 1 - c$. At an initial state with a non-negligible pest population per plant and a relative low allelic resistance (N_0, p_{r0}) it is optimal to set $q(t) = 0$ for a certain period of time, say $[t_0, t_1)$. The state path evolves to the north-west, and hits the switching curve $\Omega(t) = 0$ at time, say, t_1. A singular control will apply from there on, with $q(t) \leq 1 - c$. Notice that an instant after the switching function has been hit, say at $t_1{}^+$ the $\dot{N} = 0$ isocline will lie to the right of its initial position, having a less concave shape. The state variables (N, p_r) evolve along the switching function in the north-east direction, such that the increasing level of allelic resistance mandates higher levels of the refuge area. This behavior implies a continuous pivoting movement of the $\dot{N} = 0$ isocline around point $S1$. As the singular control $\hat{q}$ increases further and eventually converges to $1 - c$, the $\dot{N} = 0$ isocline will become the vertical line passing through $N^{Si} = g(1-c)/\gamma$.[15]

We finally discuss how the location of the switching curve with $\Omega(t) = 0$ is

[14] Some discontinuities occur with respect to the control variable, particularly before convergence occurs. The control however remains piecewise continuous, which is required by optimal control theory. We believe that this only represents a numerical artefact.

[15] If the initial state (N_0, p_{r0}) were to lie in the vicinity of the switching function and to the right of Si, we conjecture that the biological system converges on the switching locus towards the interior steady state, with values of the singular control $\hat{q} \geq 1 - c$. As this corresponds to relatively high values of allelic resistance for which no evidence exists, we neglect this possibility.

affected by a change in the bio-economic parameters.[16] In Figure 3.11 we draw the switching curve in space $N \times p_r$ when the fitness cost changes. Below the switching curve, only *Bt*-seed is planted, while above that curve no *Bt*-seed is planted in the social optimum. Figure 3.11 shows an upward shift in the switching curve when the fitness cost decreases. Thus the region where it is socially optimal to set $q = 0$ increases. This implies that for lower levels of the fitness cost, it is optimal to set $q = 0$ for lower threshold levels of the pest population N given a level of allelic resistance p_r. An interpretation for this is that lower fitness costs go hand in hand with a faster increase in the pest population (the average fitness of the overall population increases), which can only be slowed down by making more use of *Bt*-corn.

Figure 3.12 shows the effect of an increase in the supplemental cost of *Bt*-corn ($\tilde{c}_1$) on the switching curve. As can be expected, an increase in $\tilde{c}_1$ decreases the region where $q = 0$ is optimal. For a given level of allelic resistance, a higher level of the pest population is necessary to justify the complete absence of a refuge zone.

Finally, an increase in the level of the discount rate ρ leads to an upward shift in the switching curve as shown in Figure 3.13. As less weight is attributed to future costs, creating no refuge is justified only for higher levels of allelic resistance, at given levels of the pest population.[17]

The preceding discussion shows that the steady state will remain of type Si for all the parameter configurations considered here. Graphically, it is given by the intersection of the switching line and the vertical line passing through $N^{Si} = g(1 - c)/\gamma$. (For the baseline parameters stated in table 3.1, we have $N^{Si} = 1.43$). It is clear that different outcomes may arise for different parameter values. A sufficiently high additional cost of *Bt*-seed for instance will render its use unfavorable to society,

[16] As was already stated, we implicitly allow for "thick" switching curves. The contour line shown in the following figures corresponds to the level where the singular control takes the critical level $\hat{q} = 1 - c$.

[17] Results seem ambiguous for values of the pest population below one. This, we believe, is due to the fact that we have allowed for the switching curve to be a "thick" line, with the result that a certain level of inaccuracy may become apparent when the switching functions lie closely together.

such that the bio-economic system would tend to the steady state $S0$, at which the gene pool is completely susceptible to the GM crop.

3.5 Conclusion

In this paper we have addressed the use of a refuge area to control for the susceptibility of a pest population's gene pool with respect to a GM crop, notably *Bt*-seed. The objective is the minimization of the discounted social cost, consisting of the crop damage caused by the pest population and the supplemental cost of using *Bt*-seed. We have considered two different types of control. One that is restricted to remain constant over time, as well as one which may change over time. For the calibrated model, it turns our that for a time-invariant refuge area, it is optimal to exhaust the susceptibility of the gene pool completely. Such a steady state is reached for most of the parameter configurations under consideration here. Only for sufficiently high levels of the supplemental cost of *Bt*-seed will the refuge area be equal or higher than the critical level which allows to avoid a rise of pest resistance. That critical level is such that the induced natural selection of resistant pests is exactly compensated by the over-mortality of those pests, which is captured by their fitness cost.

For the case where the refuge area is allowed to vary over time, we formulate the optimal control problem. We show that the socially optimal control consists of a combination of extreme and singular controls and that the bio-economic system converges to a steady state, where the susceptibility of the gene pool is renewable. For the calibrated model, the time-variable refuge zone lowers the social costs by a magnitude of 6% as compared to the time-invariant refuge zone.

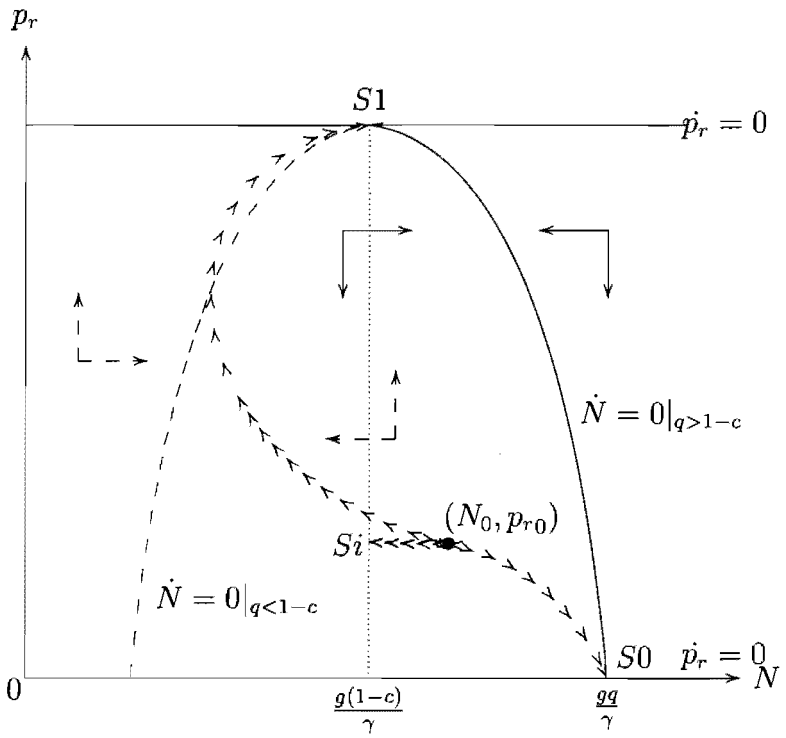

Figure 3.1: The phase diagram

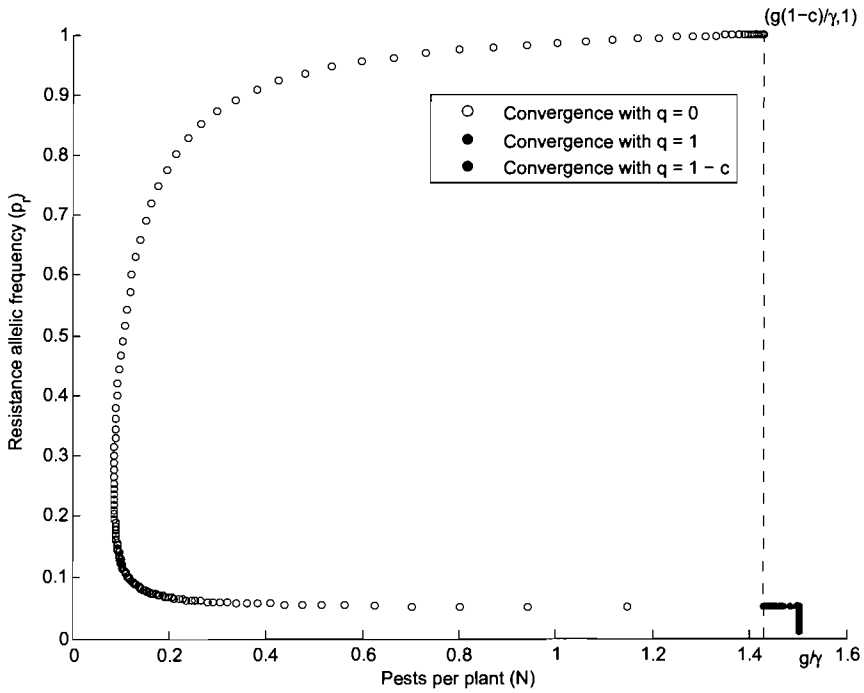

Figure 3.2: Benchmark dynamics

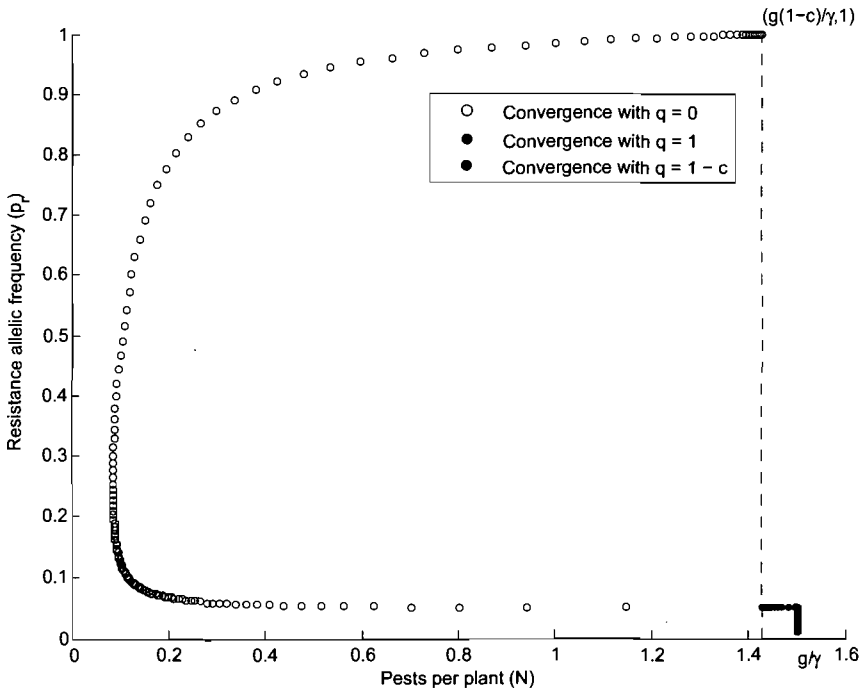

Figure 3.2: Benchmark dynamics

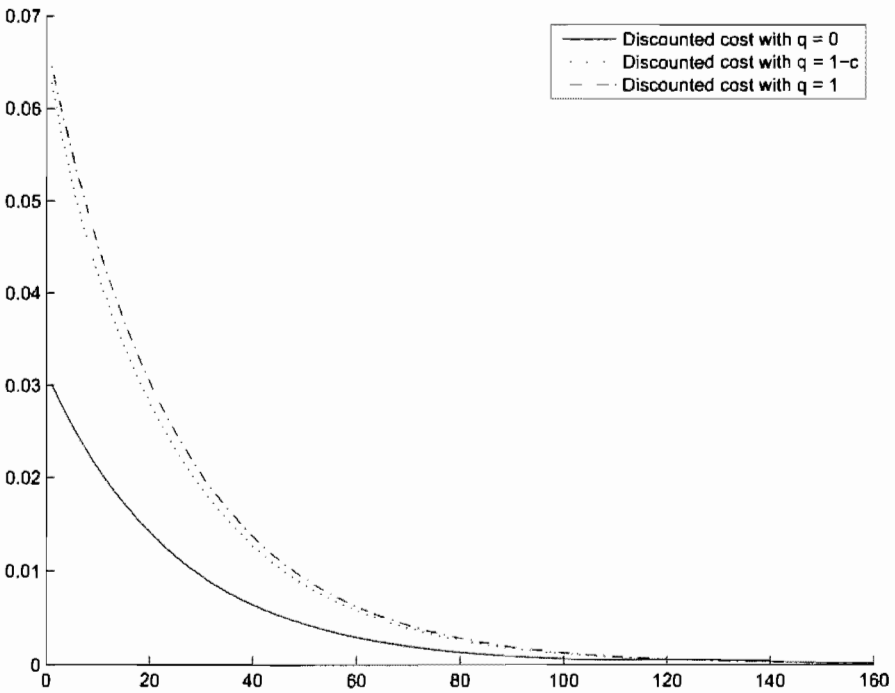

Figure 3.3: Evolution of discounted costs

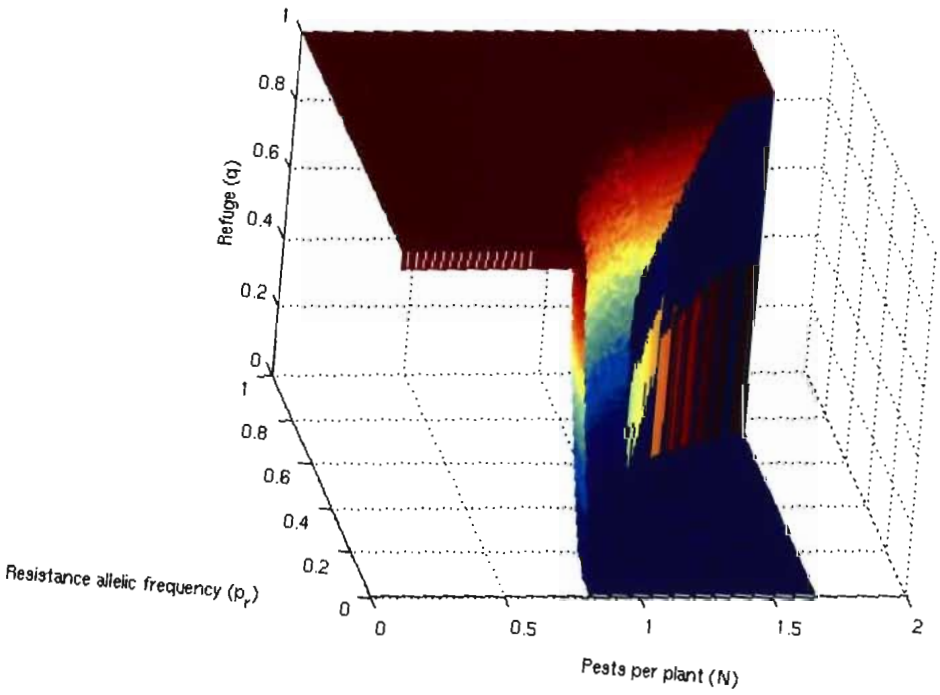

Figure 3.4: Policy function

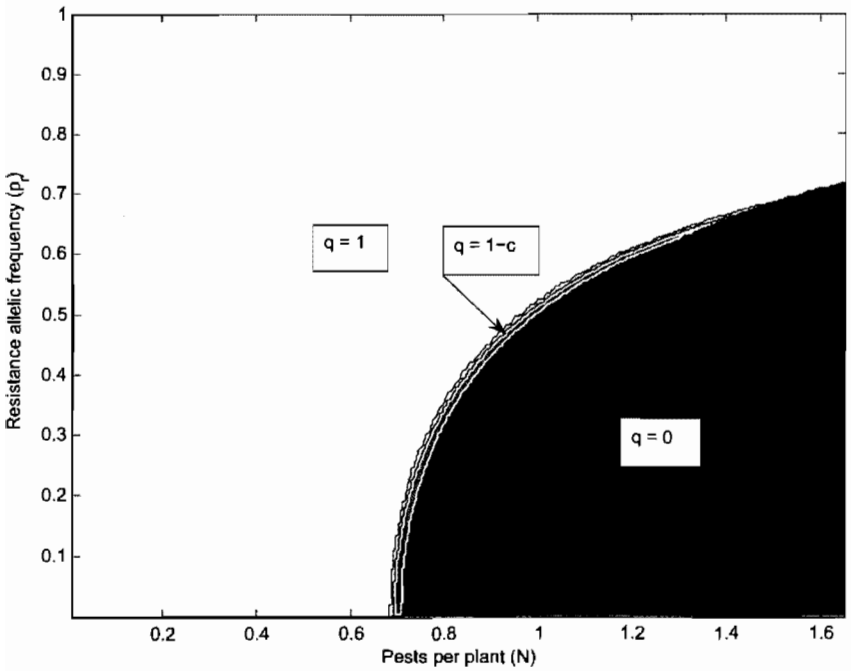

Figure 3.5: Policy contour lines

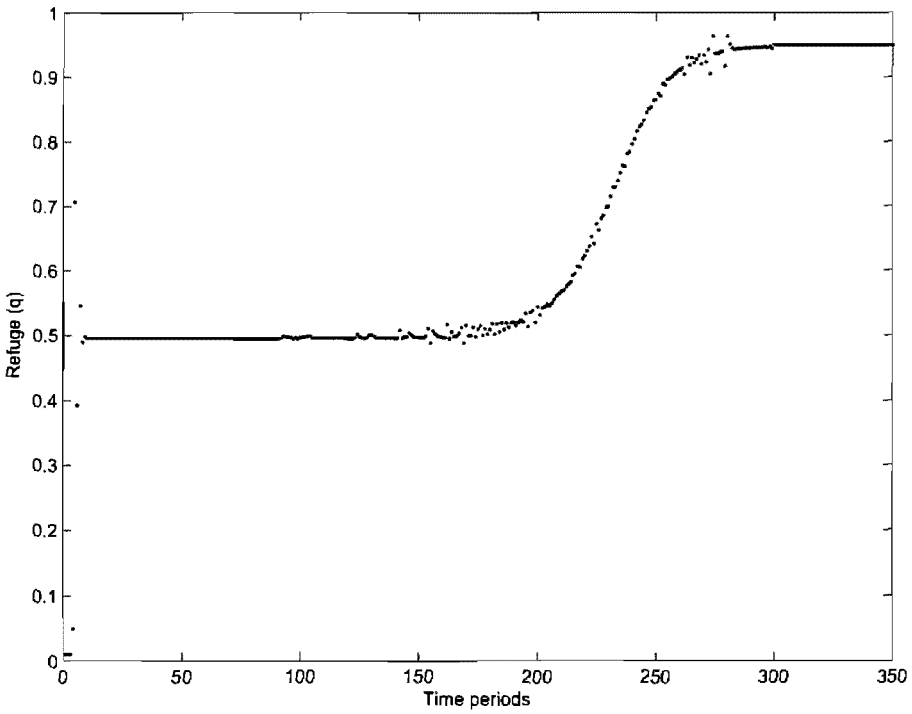

Figure 3.6: Socially optimal trajectory of refuge (q)

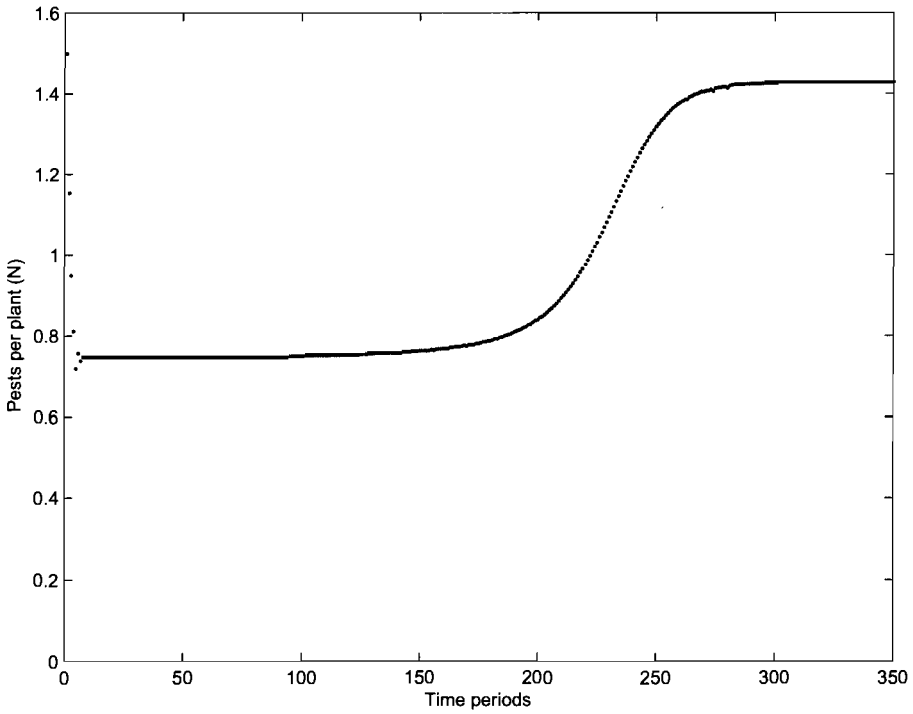

Figure 3.7: Socially optimal state path (N)

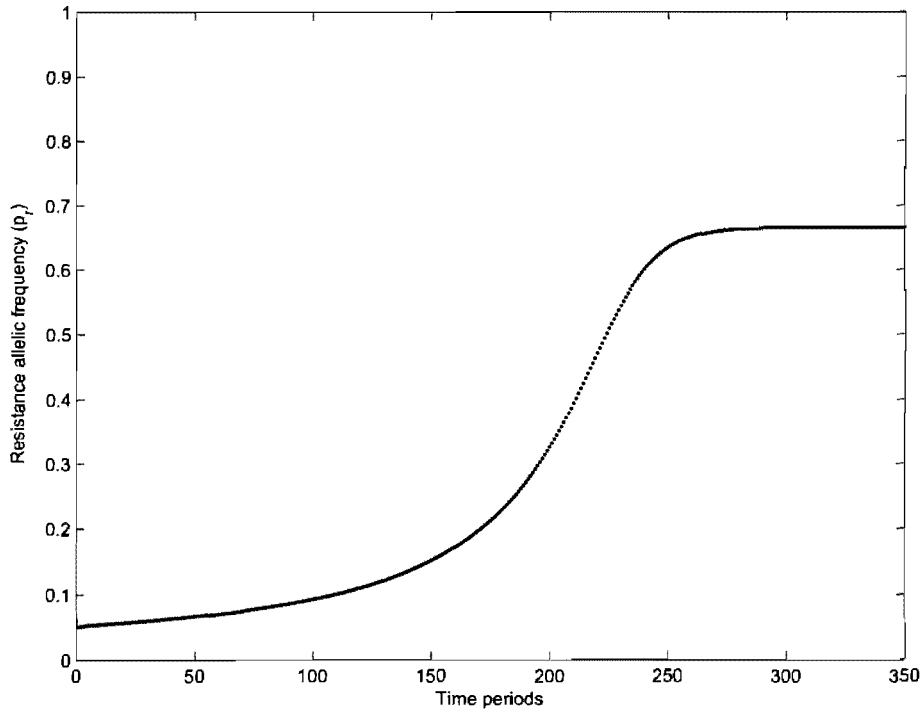

Figure 3.8: Socially optimal state path (p_r)

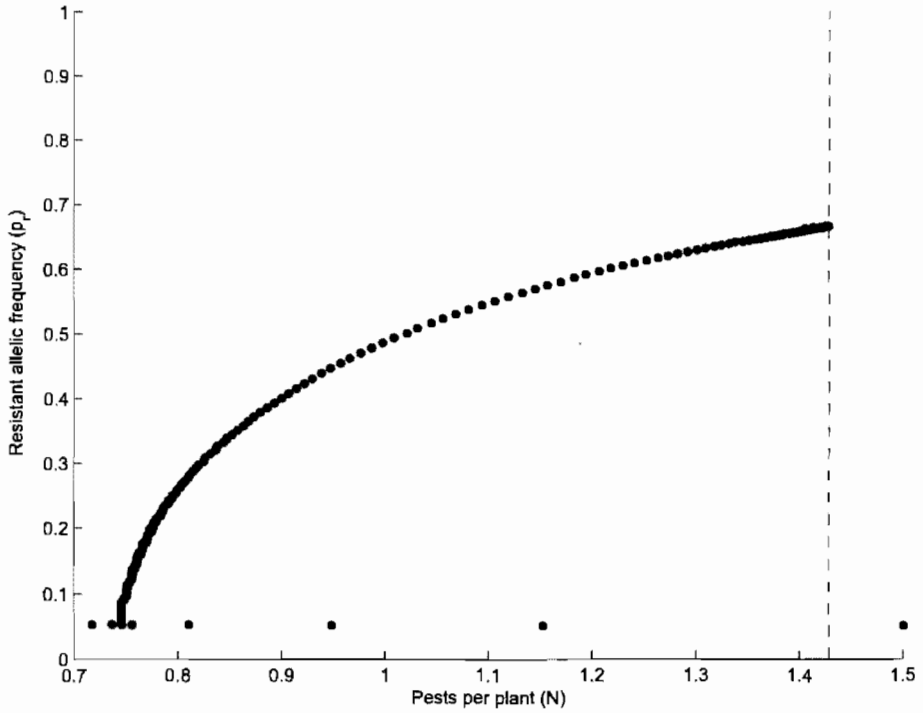

Figure 3.9: Socially optimal path (N, p_r)

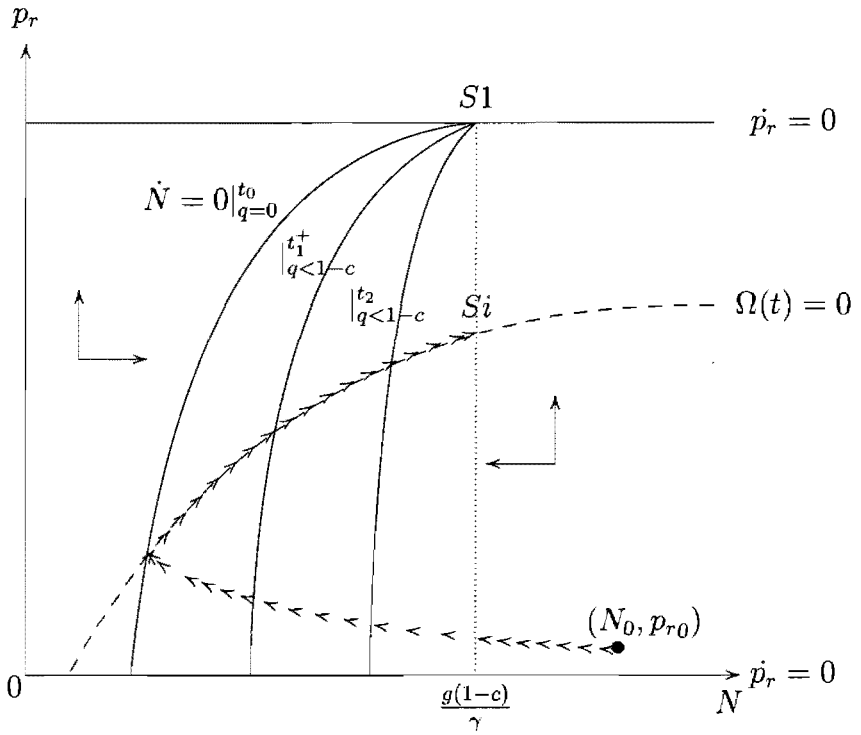

Figure 3.10: Switching function $\Omega(t)$ and dynamic convergence

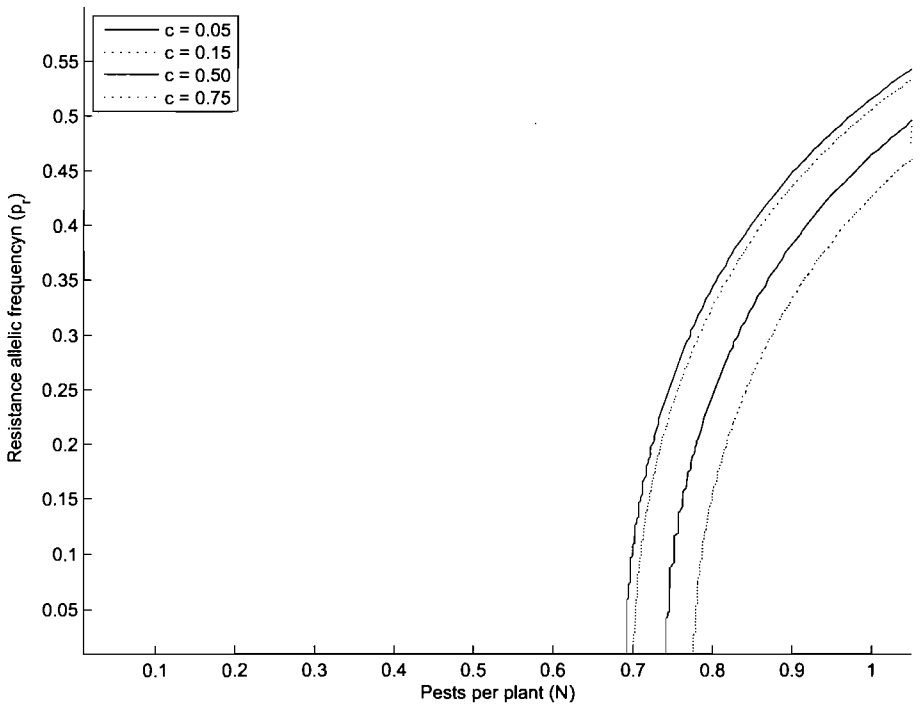

Figure 3.11: Switching curve $\Omega(t) = 0$ and the fitness cost c

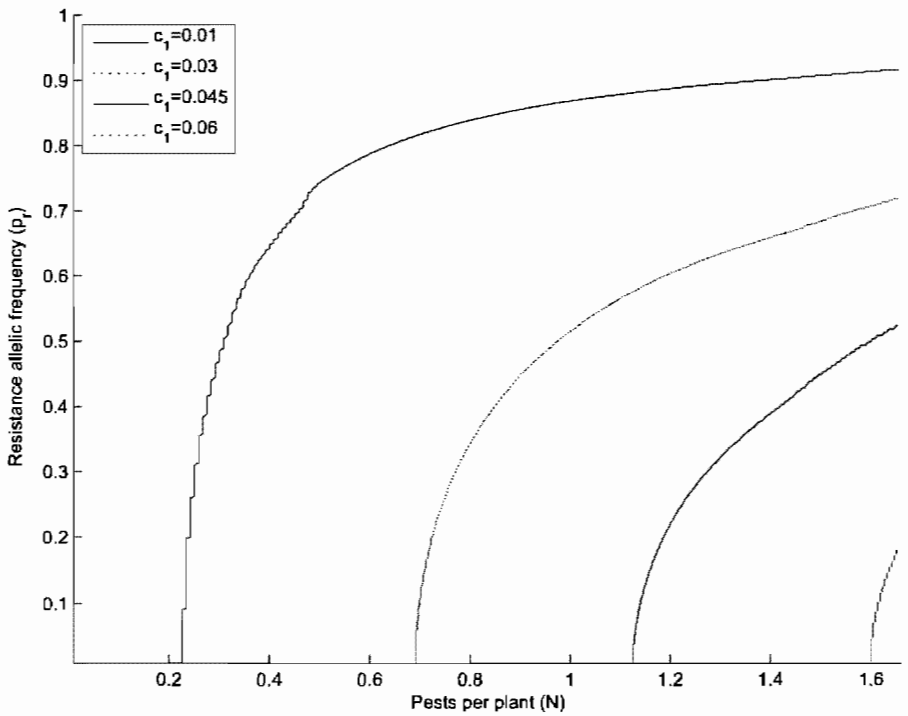

Figure 3.12: Switching curve $\Omega(t) = 0$ and the additional cost $\tilde{c}_1$

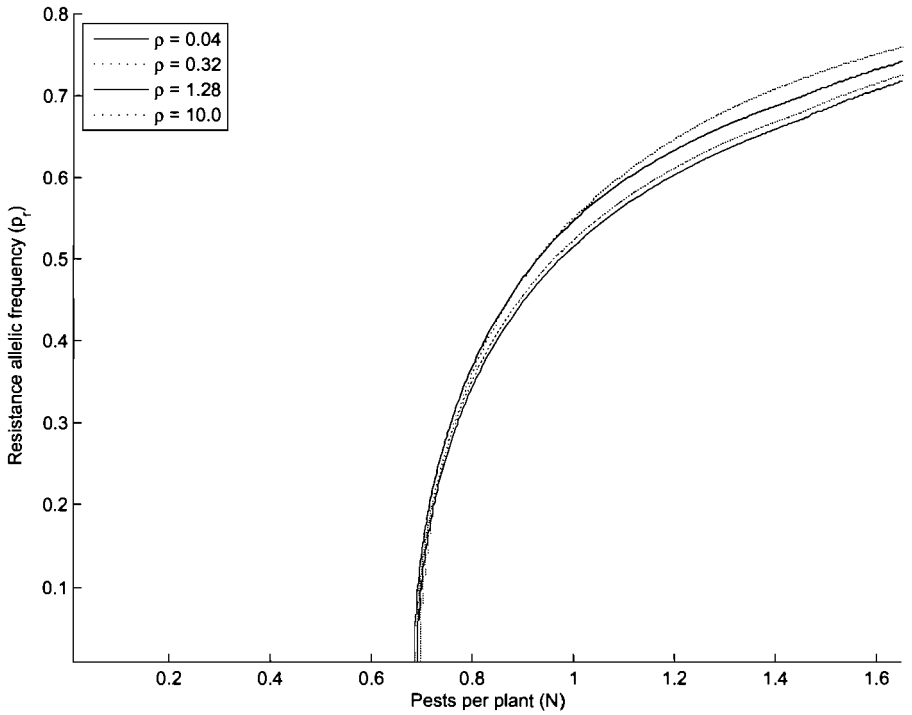

Figure 3.13: Switching curve $\Omega(t) = 0$ and the discount rate ρ

CONCLUSION

Dans cette thèse, nous avons analysé la dynamique économique d'un traitement antibiotique et d'un organisme génétiquement modifié (OGM) quand leur utilisation peut engendrer une perte d'efficacité. Plus particulièrement, nous avons caractérisé l'exploitation de l'efficacité d'un antibiotique par un marché qui se constitue d'un monopole bénéficiant d'un brevet, suivi d'une industrie vendant une version générique de l'antibiotique. L'optimum social en a également été caractérisé. Pour ce qui est de l'efficacité d'un OGM visant à combattre une population de nuisibles, nous nous sommes concentrés sur l'optimum social. Le point commun des modèles biologiques utilisés est qu'ils permettent de considérer comme une ressource renouvelable l'efficacité du traitement antibiotique d'une part, ainsi que la sensibilité du pool génétique d'insectes nuisibles à un OGM d'autre part.

Dans le premier chapitre, nous avons modélisé une industrie générique qui vend un antibiotique destiné à combattre une infection bactériologique. Cette industrie est constituée de firmes qui ont un accès libre au stock commun d'efficacité de l'antibiotique. Dans leur prise de décision, ces firmes ne tiennent compte que de l'état courant de l'efficacité de l'antibiotique et de la population infectée, négligeant l'effet de leurs décisions sur les états futurs. L'équilibre du marché est alors caractérisé par l'égalité du prix au coût moyen. Pour des fins de référence, nous avons également modélisé l'optimum social, qui tient compte du bien-être de tous les individus, infectés et non-infectés, du surplus de l'industrie, ainsi que de l'externalité reliée à la consommation de l'antibiotique.

Nous montrons que le niveau d'efficacité de l'antibiotique atteint à l'état stationnaire peut être selon les paramètres bio-économiques supérieur ou inférieur au niveau d'état stationnaire socialement optimal. Les paramètres clés sont le coût de production ainsi que le taux de guérison supplémentaire dû à la prise de l'antibiotique. Ainsi, si le taux de guérison supplémentaire est relativement élevé comparativement au coût de production, l'état stationnaire de l'efficacité de l'antibiotique atteint en optimum social est plus élevé que celui atteint en accès

libre. Le contraire est vrai si le taux de guérison additionnel est relativement faible. Cependant, la fraction de la population infectée achetant l'antibiotique ainsi que la population infectée elle-même sont identiques à l'état stationnaire sous les deux régimes.

Nous montrons qu'il existe aussi une configuration particulière de paramètres qui fait coïncider l'état stationnaire atteint en accès libre et en optimum social; la trajectoire qui y mène sous chaque régime sera cependant différente. Ceci est dû à la présence d'externalités dynamiques. Premièrement, traiter des individus au delà du niveau auquel la volonté marginale à payer égalise le coût marginal de production, serait non-profitable pour une firme en accès libre, mais peut être socialement optimal si cela permet de diminuer davantage le niveau d'infection présent et futur. Cette externalité fait en sorte que l'industrie générique tend à sous-utiliser l'antibiotique. Deuxièmement, la valeur implicite associée à l'efficacité de l'antibiotique augmente son coût d'utilisation. Puisqu'elle ne tient pas compte de cette externalité, l'industrie générique tend à sur-utiliser l'antibiotique. Laquelle de ces externalités domine dépend des paramètres bio-économiques.

Dans le deuxième chapitre, nous avons modélisé l'exploitation de l'efficacité de l'antibiotique par un monopole bénéficiant d'un brevet. Nous supposons que le monopoleur se comporte comme une firme en accès libre une fois le brevet échu. Ceci nous a permis de caractériser la politique de prix du monopoleur.

Contrairement à un producteur myope, le monopoleur tient compte des externalités dynamiques lors de sa prise de décision sur le prix et gère, de cette manière, sa taille de marché et la qualité de l'antibiotique. Ainsi, dans le but de maximiser ses profits inter-temporels, le monopoleur génère par sa politique de prix des niveaux généralement plus élevés de la population infectée et de l'efficacité de l'antibiotique, si on les compare à ceux qui seraient atteints par un monopoleur myope. Plus particulièrement, nous avons montré que le système bio-économique est caractérisé par une propriété de *turnpike*. Ceci signifie que le prix s'approche du voisinage du prix d'état stationnaire qui serait atteint par un monopoleur bénéficiant d'un brevet de durée infinie et y demeure durant un intervalle de temps

qui dépend de la durée de vie du brevet. A l'approche de la date d'expiration du brevet, le monopoleur se comporte de façon de plus en plus myope. Ceci se reflète dans une diminution continue du prix, jusqu'à ce que la recette marginale égalise le coût marginal de production. Ce mouvement est accompagnée d'une diminution de la population infectée et, généralement, par une diminution du niveau de l'efficacité de l'antibiotique. Au moment de l'expiration du brevet, le monopoleur accorde une valeur implicite nulle à la taille du marché et à la qualité de l'antibiotique. Avec l'arrivée de l'industrie générique, une chute du prix survient, menant ainsi à une hausse de la fraction de la population infectée qui achète l'antibiotique. Le bio-système évolue ensuite de la manière décrite dans le premier chapitre pour atteindre un nouvel équilibre de long terme.

Dans le troisième chapitre, nous avons modélisé la sensibilité à un OGM d'une population de nuisibles qui peut être gérée à l'aide d'une zone de refuge. L'objectif est de minimiser la valeur présente du coût associé à la perte de récolte due aux nuisibles ainsi que le coût supplémentaire associé à l'utilisation de l'OGM. Nous montrons que l'état stationnaire atteint par une zone de refuge variable dans le temps est généralement caractérisé par un niveau de sensibilité de ce pool qui se situe entre 0% et 100% de la surface totale. Il y aura alors présence de gènes résistants à l'OGM, mais sans qu'ils ne dominent le bio-système à long terme. Cette zone de refuge socialement optimale est une combinaison d'un contrôle extrême et singulier. Par contre, si la zone de refuge est contrainte à être constante dans le temps, la convergence vers un tel état stationnaire nécessite une configuration très particulière de paramètres bio-économiques, à savoir un taux d'actualisation social nul ou un coût d'utilisation de l'OGM relativement élevé comparé au coût calibré.

Pour une zone de refuge invariable dans le temps, nous trouvons, pour le modèle calibré ainsi que la grande majorité de configurations de paramètres considérés, que le système bio-économique converge vers un état stationnaire dans lequel la sensibilité du pool génétique est complètement épuisé, de sorte que l'OGM perd son efficacité à long terme. Le coût social associé à une zone de refuge constante dans le temps est de 6% plus élevé que celui associé à une zone de refuge qui peut

varier.

Cette thèse a abordé la perte potentielle d'efficacité d'un traitement antibiotique et d'un OGM comme un problème d'exploitation d'une ressource renouvelable d'un point de vue économique. L'approche retenue nous a permis de caractériser la gestion socialement optimale de ces ressources biologiques et de faire ressortir plusieurs externalités dont un marché ne tient pas nécessairement compte. Une piste de recherche future consisterait à analyser des outils économiques visant à corriger ces externaltités.

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Annexe I

Appendix of chapter 1

We first recall the full dynamic system, involving the state and co-state variables, which the socially optimal solution must satisfy. It is given by:

$$\dot{w} = w(1-w)(\Delta r - r_f f) \tag{I.1}$$

$$\dot{I} = I(\beta(N-I) - r_r + w(\Delta r - r_f f)) \tag{I.2}$$

$$\dot{\mu} = \rho\mu + \frac{1}{2}\Delta r I - r_f f I + \frac{1}{2} r_f f^2 I - (\Delta r - r_f f)[\mu(2w-1) - \lambda I] \tag{I.3}$$

$$\dot{\lambda} = \rho\lambda + \frac{1}{2}(1-\pi(w)) - r_f w f + \frac{1}{2} r_f w f^2 + cf$$
$$-\lambda[\beta(N-2I) - r_r + w(\Delta r - r_f f)] \tag{I.4}$$

In addition, the first-order condition (1.26) for the maximization of the Hamiltonian must be satisfied at every point in time, including at a steady state. A steady state solution is given by $\dot{w} = \dot{I} = \dot{\mu} = \dot{\lambda} = 0$.

I.1 The socially optimal steady state with $w^{SS^*} = 1$

Setting $w = 1$ in (II.1), we have $\dot{w} = 0$. Setting $\dot{I} = 0$, $\dot{\lambda} = 0$ and $w = 1$ in (II.2) and (II.4) gives:

$$I = \frac{\beta N - r_w - r_f f}{\beta} \tag{I.5}$$

$$\lambda = \frac{f(r_f - c) - \frac{1}{2} r_f f^2 - \frac{1}{2}(1 - r_w)}{\rho + \beta I} \tag{I.6}$$

For convenience, we rewrite the first-order condition (1.26) as:

$$r_f I(1 - \frac{c}{r_f} - f - \lambda) + \sigma_0 - \sigma_1 = 0 \tag{I.7}$$

where σ_0 and σ_1 are the Lagrange multipliers associated to the constraints $f \geq 0$ and $f \leq 1$ respectively and

$$\sigma_0 f = 0, \quad \sigma_1(1-f) = 0, \quad \sigma_0 \geq 0, \quad \sigma_1 \geq 0.$$

Equation (I.5), (I.6) and (I.7) together determine I^{SS^*}, λ^{SS^*} and f^{SS^*}.

Setting $f = 0$, we find:

$$\sigma_0 = -\frac{r_f(\beta N - r_w)}{\beta}\left(1 - \frac{c}{r_f} + \frac{1-r_w}{2(\beta N - r_w + \rho)}\right).$$

This expression is negative if $c \leq r_f$. This means that if $c \leq r_f$ the treatment rate must be positive, since σ_0 must be non-negative. However if $c > r_f$, then for c sufficiently high the expression in parentheses will be negative and σ_0 will be positive, which means that the optimal treatment rate is $f = 0$. In fact, we must have

$$f > 0 \quad \text{if} \quad c < \left(1 + \frac{1-r_w}{2(\beta N - r_w + \rho)}\right) r_f$$

and

$$f = 0 \quad \text{if} \quad c > \left(1 + \frac{1-r_w}{2(\beta N - r_w + \rho)}\right) r_f > r_f$$

.

Setting $f = 1$, we find:

$$\sigma_1 = -\frac{\beta N - r_w - r_f}{\beta}\left(c + \frac{\frac{1}{2}r_f - c - \frac{1}{2}(1-r_w)}{\beta N - r_w - r_f + \rho} r_f\right) \tag{I.8}$$

Clearly there exist admissible values of the parameters for which $\sigma_1 \geq 0$ and $f = 1$ is a solution.

An interior solution for f must satisfy (I.5), (I.6) and (I.7) with $\sigma_0 = \sigma_1 = 0$. It is easy to verify numerically that there exist values of the parameters for which the solution for f is interior.

We therefore conclude that f^{SS^*} can take any value from zero to one, with the exact value depending on the set of parameters.

I.2 The socially optimal steady state with $f^{SS^*} = \frac{\Delta r}{r_f}$

For an interior solution to the maximization of the Hamiltonian, f must satisfy equation (1.29), in addition to (II.1)-(II.4). Setting $f = f^{SS^*} = \Delta r / r_f$, we have $\dot{w} = 0$, from (II.1), and from (II.2):

$$I^{SS^*} = \frac{\beta N - r_r}{\beta}. \tag{I.9}$$

Setting $\dot{\mu} = 0$ in (II.3) and substituting for f^{SS^*} and I^{SS^*}, we get the steady-state solution for μ:

$$\mu^{SS^*} = \frac{\Delta r}{2\rho}\left[1 - \frac{\Delta r}{r_f}\right]\left[\frac{\beta N - r_r}{\beta}\right]. \tag{I.10}$$

We still need to determine the steady-state levels of antibiotic efficacy, w^{SS^*}, and of the shadow cost of infection, λ^{SS^*}. Setting $\dot{\lambda} = 0$ in (II.4) and substituting for f^{SS^*} and I^{SS^*} we get:

$$\lambda = \frac{\frac{1}{2}(r_r - 1) - \frac{c}{r_f}}{\rho + \beta N - r_r} + \frac{\frac{1}{2}\Delta r\left[1 - \frac{\Delta r}{r_f}\right]}{\rho + \beta N - r_r} w \tag{I.11}$$

which is a positively-sloped straight line in (w, λ) space.

Substituting for f^{SS^*} and I^{SS^*} into (1.29), we get:

$$\lambda = \left[1 - \frac{\Delta r}{r_f}\right]\left(1 - \frac{\Delta r}{2\rho}\right) - \frac{c}{r_f}\frac{1}{w} + \frac{\Delta r}{2\rho}\left[1 - \frac{\Delta r}{r_f}\right] w \tag{I.12}$$

which represents a hyperbola with a vertical asymptote at $w = 0$ and an oblique asymptote with a positive slope. These two curves will intersect to the right of the vertical asymptote, *i.e.* where $w > 0$. This is because the ratio of the slope of the oblique asymptote and the slope of (II.14) is $(\rho + \beta N - r_r)/\rho > 1$ and the hyperbola (I.12) approaches its oblique asymptote from below. The point of intersection yields w^{SS^*}, which is given by:

$$w^{SS^*} = -\frac{J}{2H} + \sqrt{\left(\frac{J}{2H}\right)^2 - \frac{K}{H}} \tag{I.13}$$

where

$$\begin{aligned} H &= (r_f - \Delta r)\frac{\Delta r(r_r - \beta N)}{2\rho} \\ J &= (r_f - \Delta r)(\rho + \beta N - r_r)\left(\frac{\Delta r}{2\rho} - 1\right) + \frac{r_f}{2}(r_r - 1) - c\Delta r \\ K &= c(\rho + \beta N - r_r). \end{aligned}$$

Depending on the set of parameters we have $w^{SS^*} < 1$ or $w^{SS^*} = 1$. The analysis of the parameter space concentrates on the space $(r_f, c) \in (\Delta r, \beta N - r_w] \times (0, \infty)$. The lower bound on r_f guarantees that $\Delta r / r_f < 1$, which implies that the level of antibiotic efficacy decreases if the whole infected population is treated. There exists an arbitrage between keeping the level of efficacy high and keeping that of infection low. The upper bound on r_f guarantees that the level of infection is non-negative at $f = 1$ in the steady state defined by (1.7). The admissible interval for c guarantees that the unit cost of production is positive, as assumed.

From (I.13) we find that $w^{SS^*} = 1$ implies:

$$c = \tilde{c}(r_f) = \frac{\Delta r\left[\frac{\Delta r}{2} - (\beta N - r_r + \rho)\right]}{\beta N - r_r + \rho - \Delta r} + \left(\frac{\beta N - r_r + \rho + \frac{1}{2} - \frac{1}{2}(\Delta r + r_r)}{\beta N - r_r + \rho - \Delta r}\right) r_f. \tag{I.14}$$

This equation represents a straight line that divides the (r_f, c)-space. Everything else equal, for a small enough fitness cost we have $\beta N - r_r + \rho - \Delta r > 0$ and this line is then positively-sloped and has a negative intercept. We then have $w^{SS^*} < 1$ below the line and $w^{SS^*} = 1$ above it.

Annexe II

Appendix of chapter 2

We first recall the full dynamic system, involving the state and co-state variables, which the monopoly solution must satisfy. It is given by:

$$\dot{w} = w(1-w)(\Delta r - r_f f) \tag{II.1}$$

$$\dot{I} = I(\beta(N-I) - r_r + w(\Delta r - r_f f)) \tag{II.2}$$

$$\dot{\mu} = \rho\mu + (\Delta r - r_f f)[\mu(2w-1) - \lambda I] - r_f I(1-f)f \tag{II.3}$$

$$\dot{\lambda} = \rho\lambda + \lambda[2\beta I - \beta N + r_r - w(\Delta r - r_f f)] - r_f w(1-f)f + cf \tag{II.4}$$

In addition, the first-order condition (2.12) for the maximization of the Hamiltonian must be satisfied at every point in time, including at a steady state. A steady-state solution is given by $\dot{w} = \dot{I} = \dot{\mu} = \dot{\lambda} = 0$.

II.1 The steady state with $w^{SS} = 1$

Setting $w = 1$ in (II.1), we have $\dot{w} = 0$. Setting $\dot{I} = 0$, $\dot{\lambda} = 0$ and $w = 1$ in (II.2) and (II.4) gives:

$$I = \frac{\beta N - r_w - r_f f}{\beta} \tag{II.5}$$

$$\lambda = \frac{r_f(1-f)f - cf}{\rho + \beta I} \tag{II.6}$$

For convenience, we rewrite the first-order condition in (2.17) evaluated at $w^{SS} = 1$

$$r_f w(1-2f) = c + r_f w\lambda. \tag{II.7}$$

Replacing (II.6) into (II.7) gives an expression in the treatment rate f, which we solve for to obtain:

$$f_{1,2} = \frac{a}{2} \pm \sqrt{\left(\frac{a}{2}\right)^2 - b} \tag{II.8}$$

where

$$a = \frac{2}{3r_f}[\rho + \beta N - r_w + r_f - c] \tag{II.9}$$

$$b = \frac{\left(1 - \frac{c}{r_f}\right)(\rho + \beta N - r_w)}{3r_f} \tag{II.10}$$

Both values of $f_{1,2}$ are admissible solutions, and we cannot exclude any of them analytically. Our numerical simulations however suggest that the solution is unique and given by:

$$f^{SS} = \frac{a}{2} - \sqrt{\left(\frac{a}{2}\right)^2 - b} \tag{II.11}$$

II.2 The intermediate steady state with $f^{SS} = \frac{\Delta r}{r_f}$

For an interior solution to the maximization of the Hamiltonian, f must satisfy equation (2.17), in addition to (II.1)-(II.4). Setting $f = f^{SS} = \Delta r / r_f$, we have $\dot{w} = 0$, from (II.1), and from (II.2):

$$I^{SS} = \frac{\beta N - r_r}{\beta}. \tag{II.12}$$

Setting $\dot{\mu} = 0$ in (II.3) and substituting for f^{SS^*} and I^{SS^*}, we get the steady-state solution for μ:

$$\mu^{SS} = \frac{\Delta r}{r_f} \frac{I^{SS}(r_f - \Delta r)}{\rho} \tag{II.13}$$

We still need to determine the steady-state levels of antibiotic efficacy, w^{SS}, and of the shadow price of infection, λ^{SS}. Setting $\dot{\lambda} = 0$ in (II.4) and substituting for f^{SS} and I^{SS} we get:

$$\lambda = \frac{\Delta r}{r_f} \frac{w(r_f - \Delta r) - c}{\rho + \beta N - r_r}. \tag{II.14}$$

Since $f^{SS} = \Delta r/r_f$ is the monopoly solution in this steady state, price $p = r_f w(1 - \Delta r/r_f)$ must be higher than the marginal production cost c, implying a positive value of λ. Substituting for f^{SS}, I^{SS}, μ^{SS} and λ from (II.14) into (2.17), we get a binomial in w, the solutions of which are:

$$w = -\frac{B}{2A} \pm \sqrt{\frac{c}{A} + \left(\frac{B}{2A}\right)^2} \tag{II.15}$$

where

$$\begin{aligned} A &= \Delta r(r_f - \Delta r)\frac{\beta N - r_r}{\rho(\rho + \beta N - r_r)} \\ B &= (r_f - 2\Delta r) - \Delta r\frac{r_f - \Delta r}{\rho} + \frac{\Delta r c}{\rho + \beta N - r_r}. \end{aligned}$$

The expression for A is positive, while the sign of B depends on the parameters of the model. In order to exclude solutions with $w < 0$ for all B, the admissible solution for w is

$$w^{SS} = -\frac{B}{2A} + \sqrt{\frac{c}{A} + \left(\frac{B}{2A}\right)^2}. \tag{II.16}$$

Depending on the set of parameters, we have $w^{SS} < 1$ or $w^{SS} = 1$. The condition $w^{SS} \leq 1$ can be written as:

$$c \leq \Delta r\frac{\Delta r - 2(\rho + \beta N - r_r)}{\rho + \beta N - r_r - \Delta r} + r_f. \tag{II.17}$$

In the case of a zero fitness cost $\Delta r = 0$, the condition (II.17) becomes $c \leq r_f$, which is always verified if the antibiotic is economically viable at the maximum value of antibiotic efficacy ($w = 1$).

Annexe III

Appendix of chapter 3

III.1 Discrete-time version for numerical approximation

For numerical simulations we make use of a discrete-time version of the model given by equations (3.8) and (3.9) respectively. Following Ginzburg (1983, chapter 1), we write the discrete-time version of equation (3.8) as:

$$\Delta p_r = p'_r - p_r = p_r \frac{V_r - \bar{V}}{\bar{V}}, \tag{III.1}$$

where $V_{ij} = 1 + \epsilon_{ij}\Delta t$, and V_i and $\bar{V}$ are defined as function of V_{ij} as before, while Δt is the length of the time period. After substituting for V_r and $\bar{V}$, equation (III.1) becomes:

$$\Delta p_r = p_r^2(1 - p_r)\frac{g\Delta t(1 - c - q)}{1 + g\Delta t[q(1 - p_r^2) + (1 - c)p_r^2]} \tag{III.2}$$

The discrete-time version of equation (3.9) is given by:

$$\Delta N = N' - N = (\bar{W} - 1)N, \tag{III.3}$$

where $W_{ij} = 1 + \Delta t f_{ij}$, and W_i and $\bar{W}$ are defined as a function of W_{ij} as before. Substituting for $\bar{W}$, equation (III.3) becomes:

$$\Delta N = g\Delta t[p_r^2(1 - c - q) + q]N - \gamma\Delta t N^2 \tag{III.4}$$

III.2 Approximation of the two pest generations per season model

Let g_1 and g_2 denote the two successive generations of insects and let t denote the year in the simulation model of Hurley *et al.* (2001). Assuming heavy suppression in their simulation model in the absence of *Bt* plantings, the population of the

second generation in year $t+1$ is determined as a function of the population of the second generation in year t by two successive logistic equations:

$$\begin{aligned} N_{t+1,g_1} &= 0.243N_{t,g_2} - 0.053\left(N_{t,g_2}\right)^2 \\ N_{t+1,g_2} &= 8.76N_{t+1,g_1} - 10.30\left(N_{t+1,g_1}\right)^2, \end{aligned}$$

or equivalently:

$$N_{t+1,g_2} = 8.76\left[0.243N_{t,g_2} - 0.053\left(N_{t,g_2}\right)^2\right] - 10.\left[0.234N_{t,g_2} - 0.053\left(N_{t,g_2}\right)^2\right]^2.$$

We approximate this equation using OLS with the logistic function:

$$N_{t+1,g_2} = 1.94N_{t,g_2} - 0.625\left(N_{t,g_2}\right)^2,$$

which gives the evolution of the pest population in the absence of *Bt*-plantings. We then have $0.94 = g(1 - cp_{r_0}^2) \approx g$ and $0.625 = \gamma$.