J. Math. Biol. 43, 52–68 (2001)
Digital Object Identifier (DOI):
10.1007/s002850100092

Mathematical Biology

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The influence of drug treatment on the maintenance of schistosome genetic diversity

Received: 15 May 2000 / Revised version: 8 November 2000 /
Published online: 18 June 2001–

Abstract. Drug treatment of patients with schistosomiasis may select for drug-resistant parasites. In this article, we formulate a deterministic model with multiple strains of schistosomes (helminth parasites with a two-host life cycles) in order to explore the role of drug treatment in the maintenance of a polymorphism of parasite strains that differ in their resistance levels. The basic reproductive numbers for all strains are computed, and are shown to determine the stabilities of equilibria of the model and consequently the distribution of parasite phenotypes with different levels of drug tolerance. Analysis of our model shows that the likelihood that resistant strains will increase in frequency depends on the interplay between their relative fitness, the cost of resistance, and the degree of selection pressure exerted by the drug treatments.

Introduction

The control of schistosomiasis, presumably through the development of a schistosome vaccine, remains one of the highest priorities in parasitology. In the absence of a vaccine, current control programs have focused on chemotherapy, which reduces morbidity by killing adult worms and diminishing egg deposition. Praziquantel (PZQ) remains the drug of choice for the treatment of schistosomiasis, but recent epidemiological evidence suggests the emergence of PZQ-resistant schistosomes [Cioli, 1998]. Persistent egg excretion after chemotherapy may be explained by other factors including reinfection and pre-existing immature parasites [Renganathan and Cioli, 1998], but laboratory data supports the view that selection for resistance to PZQ may be occurring in schistosome populations [Fallon et al., 1997]. It has long been known that variations in host response to chemotherapy exist within and between populations of *Schistosoma mansoni* [Araujo et al., 1980]. Recent field and laboratory data suggest that substantial levels of genetic variation are also present among natural strains of this parasite [Minchella et al., 1994, 1995]. It is likely that parasite genetic diversity underlies observed differences in PZQ resistance by schistosomes, as resistance to the drugs oxamniquine and hycanthone has been

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Key words or phrases: Schistosomiasis – Drug resistance – Genetic diversity – Coexistence – Mathematical models

documented and was found to be associated with genomic changes [Brindley et al., 1989, 1991].

Several mathematical models describing the dynamic interactions between hosts and macroparasites (parasitic helminths) have been proposed and studied (see, for example, [Anderson and May, 1978, 1979; May and Anderson, 1979; Dobson, 1988; Hadeler, 1984; Hadeler and Dietz, 1982; Roberts and Dobson, 1995]). These models do not generally include the development of parasite resistance to chemotherapy. However, the study of parasite drug-resistance is surely important both for the understanding of parasite genetic diversity and for the design of disease control strategies.

In this article, we develop a new model to study how control measures may affect parasite genetic diversity. Herein, we explore the selective forces acting on the schistosome population at a critical stage of the parasite life cycle, and consider the evolutionary dynamics of a host-parasite interaction that involves multiple parasite strains and includes both definitive and intermediate hosts. Our model assumes a simple genetic basis for drug resistance in schistosomes and explores how drug treatments may have an impact on the distribution of parasite strains. We show that if the parasite reproduction and virulence (parasite-related host death) are linked to resistance, then drug treatment may lead to the establishment of multiple parasite strains with many different levels of resistance, though we expect resistance levels to remain relatively low when this resistance has a cost to the parasites.

This paper is organized as follows: In Section 1, we formulate a mathematical model for schistosomiasis incorporating n strains ($n \geq 2$, of which $n-1$ strains are drug-resistant) of the parasites and including both the human definitive hosts and the snail intermediate hosts. Section 2 shows some numerical studies that demonstrate effects of drug treatment on asymptotic distributions of parasite strains. We devote Section 3 to an analytical understanding of the numerical observations. Particularly, we consider the case $n = 2$ with one strain being drug-sensitive and the other one resistant. We compute the basic reproductive number for each strain and some possible steady states, study the stability of the boundary steady states as well as conditions for coexistence, and derive a criterion for invasion by resistant strains. Section 4 discusses the results, including some biological interpretations of our work.

1. Model formulations

Anderson and May [1978] constructed a simple model of interactions between hosts and macroparasites. In their model, the host population size H is assumed to grow exponentially and the parasites are assumed to have a negative binomial distribution within the hosts. They demonstrated that a host population's size can be regulated by a parasite species. Dobson [1985] and Roberts and Dobson [1995] developed a multi-species version of the Anderson and May model in which the total number P_i of the parasites of species i is governed by the equation:

$$\frac{dP_i}{dt} = \frac{\lambda_i P_i H}{A+H} - (\mu_h + \mu_i + \alpha_i)P_i - \alpha_i V_i \frac{P_i^2}{H} - \sum_{j=1, j\neq i}^{n} \alpha_j L_{ij} \frac{P_i P_j}{H}, \quad i = 1, 2, \cdots, n \tag{1.1}$$

where λ_i is the per capita rate of parasite production of transmission stages of species i; μ_h is the per capita natural death rate of human hosts; μ_i is the per capita death rate of adult parasites of species i; α_i is the disease-induced death rate of humans *per parasite* (a constant determined by the pathogenicity of a parasite); A is a scaling constant; $V_i = \frac{1+k_i}{k_i}$, where k_i is the clumping parameter of the negative binomial distribution of species i; and, $L_{ij} = \frac{1+l_{ij}}{l_{ij}}$, where l_{ij} is a parameter related to the covariance of parasite distributions between species i and species j.

In this article, we extend the Dobson model to include 1) the intermediate snail hosts, 2) treatment of human hosts by chemotherapy, and 3) parasite resistance to the drug. We continue to use a convention found in many host-parasite models by assuming a negative binomial to describe the distribution of parasites within their human hosts [Poulin, 1998]. While this convention has been criticized as assuming aggregation in the face of a disease mechanism that disrupts such aggregation [Pugliese, 2000], we retain the negative binomial for several reasons. Foremost, for schistosomiasis, this distribution continues to be a good approximation of empirical data [Anderson and May, 1978; Chandiwana et al., 1991]. Furthermore, while schistosomes cause significant morbidity, they cause little direct mortality, so that the effect of non-random thinning on the negative binomial is unlikely to affect our model. Since the exact mechanisms that generate the observed distribution are unknown, it is not clear whether it is stable in the face of system-wide perturbations, such as drug treatment (given that some strains are more resistant than others), and further simulation/empirical work is required in this area. We must then proceed with the further assumption that the mechanisms that generate the negative binomial distribution are relatively robust and stable to perturbations.

We examined the dynamics of our model under the default assumption $L_{ij} = V_i = V$. Thus, the two strains are affected equally by the clustering mechanism and have the same values of V and also that the values of L_{ij} are equal to this V. Under this assumption, in the absence of drug treatment two identical parasite strains will never coexist in a stable equilibrium, and are subject to neutral drift. Mathematically, the result of neutral drift is represented by a line of neutrally stable equilibria. We show that, under the same assumption, coexistence is possible if drug treatment and resistance are incorporated in the model.

We assume that a disease control program distributes PZQ to a fraction of the population at a constant rate, but the effectiveness of the drug to kill the i-th strain of the parasites is reduced by a factor θ_i due to resistance. Notice that a parasite utilizes two hosts in its life cycle, and hence there are two transmission stages: human to snail and snail to human. Our equation for the i-th strain of parasites reads:

$$\frac{dP_i}{dt} = \frac{\lambda_i I_i H}{A+H} - (\mu_h + \mu_i + \alpha_i + \frac{\sigma}{\theta_i})P_i - \alpha_i V_i \frac{P_i^2}{H} - \sum_{j=1, j\neq i}^{n} \alpha_j L_{ij} \frac{P_i P_j}{H},$$
$$i = 1, 2, \cdots, n \qquad (1.2a)$$

where I_i denotes the number of snails infected by a parasite of strain i, σ is the treatment rate of human hosts, and λ_i is now the per capita rate of parasite production of

transmission stages from snail to human. The parameter θ_i describes the resistance level of the parasite to PZQ relative to the drug-sensitive strain. We assume that $\theta_1 < \theta_2 < \cdots < \theta_n$ with $\theta_1 = 1$ for the drug-sensitive strain. In this context, the genetic variation of the parasites (e.g., the polymorphism in the parasite population) is represented by strains with different levels of resistance to the drug. Based on the suggestion that the number of cercariae produced is independent of parasite burden of the infected snail [Woolhouse, 1991], we simply divide the snail population into two subclasses: I (infected snails) and S (uninfected snails). Because schistosomes cause infertility of snails [Minchella, 1985], we assume that infected snails do not reproduce. Under these assumptions, our equations for the snails are

$$\begin{aligned} \frac{dS}{dt} &= f(S, I_1, I_2, \cdots, I_n)S - \nu S - \sum_{i=1}^{n} \frac{\rho_i P_i S}{B+S}, \\ \frac{dI_i}{dt} &= \frac{\rho_i P_i S}{B+S} - \phi_i \nu I_i - \delta_i I_i. \end{aligned} \tag{1.2b}$$

where f is the per capita birth rate of snails; ν is the per capita death rate of snails; and, ρ_i is the per capita rate of parasite production of transmission stages from human to snail. ϕ_i corresponds to a modification in the survival of infected snails due to infection. If the infection triggers mechanisms that increase the life span of infected snails (i.e., a trade-off between reduced fecundity and increased survival [Minchella, 1985]), then ϕ_i will be smaller than one. The parameter δ_i corresponds to the parasite-induced death rate of infected snails, and this pathogenicity is assumed to operate independently of ϕ_i (see [Dobson, 1988]). We have previously considered a simpler, one-strain model with logistic growth of the snail population, and found that very complex dynamics may be expected. In this article, because we are mainly concerned with the possible effects of drug treatment on the distributions of different parasite phenotypes (as a reflection of the underlying genetics), the per capita birth rate of an uninfected snail is simply assumed to be constant, i.e., $f(S, I_1, I_2, \cdots, I_n) = b$. Notice that the difference in the average life span of humans and parasites is between one and two orders of magnitude. Consequently, during the time many generations of parasites pass, only a few generations of humans come and go. Hence we assume that the human population size remains constant.

For convenience, we introduce the following notations:

$$H_0 = \frac{H}{A+H},\ r = b - \nu,\ m_i = \mu_h + \mu_i + \alpha_i + \frac{\sigma}{\theta_i},\ u_i = \phi_i \nu + \delta_i.$$

Then (1.2a) and (1.2b) can be rewritten as

$$\begin{aligned} \frac{dP_i}{dt} &= \lambda_i H_0 I_i - m_i P_i - \alpha_i V_i \frac{P_i^2}{H} - \sum_{j=1, j\neq i}^{n} \alpha_j L_{ij} \frac{P_i P_j}{H} \\ \frac{dS}{dt} &= rS - \sum_{i=1}^{n} \frac{\rho_i P_i S}{B+S} \\ \frac{dI_i}{dt} &= \frac{\rho_i P_i S}{B+S} - u_i I_i. \end{aligned} \tag{1.3}$$

Concerning the well-posedness of the model (1.3), we just note that from the theory of systems of ordinary differential equations, we immediately have local existence and uniqueness of solutions for any non-negative initial values. Moreover, as long as they exist, solutions stay nonnegative. Using very standard estimates, one can derive *a priori* the exponential boundedness of solutions, from where the unique existence of a global solution follows.

2. Effects of drug treatment on distributions of parasite strains

Drug-resistant parasites may incur costs such as a lower reproduction rate (smaller ρ_i and λ_i). As a consequence, there may be a lower parasite-induced death rate of the snail hosts (δ_i), due to a less rapid consumption of host tissue. Notice that drug-resistance will not become an important issue when the treatment rate is very low. Therefore, throughout this article, we assume that treatment rate is high enough that drug resistance cannot be ignored, but also that costs for maintaining resistance exist. If drug resistance has a cost, then it follows that natural parasite populations in areas where a treatment program does not exist would maintain very little or no resistance. We are interested in cases where a treatment program is implemented against a formerly susceptible parasite population and the effect that this may have in increasing the frequency of drug resistance in the population. Mathematically, this is represented by a parasite population composed almost entirely of a sensitive strain ($\theta = 1$, fully susceptible) and just a few individuals with some resistance ($\theta > 1$). We can then ask questions regarding the effect of the treatment rate (σ) on the persistence of parasite strains that are paying a cost for drug resistance. One way of incorporating such effects is to assume proportionate reductions relative to the drug-sensitive strain as follows:

$$\lambda_i \rho_i = \frac{\lambda_1 \rho_1}{\theta_i}, \quad \delta_i = \frac{\delta_1}{\theta_i}, \ i = 2, 3, \cdots, n. \tag{2.1}$$

Because we are mainly interested in looking at the impact of drug treatment on distributions of parasite drug-resistance phenotypes, we assume all other parameters to have no differences among strains, i.e.,

$$\mu_i = \mu, \ \ \alpha_i = \alpha, \ \ \phi_i = \phi, \ \ V_i = V, \ \ L_{12} = L_{21} = L, \ \ i = 1, 2, \cdots, n. \tag{2.2}$$

Our numerical studies (using *Mathematica*) of the model (1.3) indicate a positive correlation between the treatment rate σ and the number of parasite strains present at equilibria as well as their abundance (see figure 1). The parameter values used in figure 1 are $\mu_h = 0.015$, $\mu = 0.175$, $\alpha = 0.01$, $b = 0.15$, $\nu = 0.1$, $\phi = 1$, $\delta_1 = 0.5$, $\rho_1 = 3$, $\lambda_1 = 50$, $A = 5000$, $B = 40000$. Figure 1 shows the equilibrium distribution of parasite strains for various values of σ between 0.1 (figure 1(a)) and 0.55 (figure 1(c)). We demonstrate our computations for $n = 3$ strains of parasites with resistance levels between 2 and 2.4: $\theta_2 = 2$, $\theta_3 = 2.2$, $\theta_4 = 2.4$. (Recall that $\theta_1 = 1$ corresponds to the drug-sensitive strain.) For these studies, we use (2.1) and (2.2), and assume $L = V = 3$. Initial values for all resistant strains are chosen to be equal and small. We observe in figure 1 that, for treatment rate σ equal to 0.2, only one resistant strain (P_2) coexists with the sensitive strain (P_1). For increasing

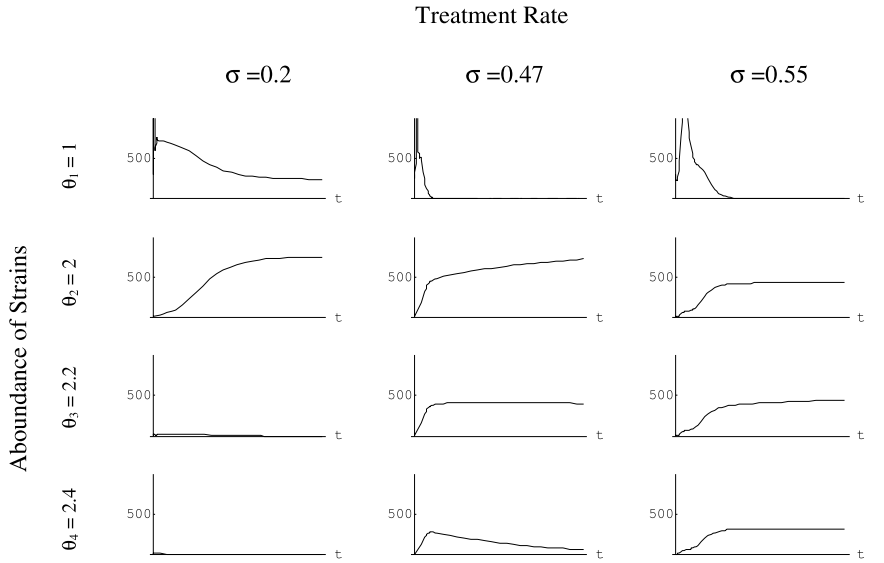

Fig. 1. Simulations of model (1.3) for various values of treatment rate σ and four parasite strains with different resistant levels. It shows plots of the number of parasites P_i vs. time. The four resistance levels are the same for all figures 1(a) – (c): $\theta_1 = 1$ (susceptible strain), $\theta_2 = 2$, $\theta_3 = 2.2$, $\theta_4 = 2.4$. (2.1) and (2.2) are used and treatment rates are $\sigma = 0.2$, 0.47, 0.55 in figures 1(a), (b), and (c), respectively. It shows that the number of resistant strains at equilibrium increases with treatment rate (e.g., one resistant strain in (a), two in (b), and three in (c)).

σ, the number of resistant strains surviving at the equilibrium also increases. When $\sigma = 0.55$, all three of the resistant strains coexist while the sensitive strain dies out. What determines the invasion and persistence of resistant strains? We derive an analytical understanding of the equilibrium structures of parasite strains in the next section.

3. Invasion of resistant strains and coexistence

Because of the complexity of the model (1.3), in deriving analytical results we consider only the case $n = 2$, i.e., P_1 denotes the drug-sensitive strain and P_2 denotes a mutant (drug-resistant) strain. Consider a situation in which the majority of parasites are drug-sensitive and a small number of individuals carry a novel mutation that confers drug resistance. Will the mutant strain invade and persist in the population? To answer this question, we first study the equilibria of (1.3) and their stabilities.

The reproductive number of the parasites of strain i is

$$\mathscr{R}_i = \frac{\lambda_i \rho_i H_0}{m_i u_i}.$$

To simplify the analysis, we rearrange the variables and let $\mathbf{U} = (S, I_1, P_1, I_2, P_2)$. System (1.3) has four possible types of equilibria:

1) parasite-free equilibrium (a pseudoequilibrium)

$$\mathbf{U}_0 = (\infty, 0, 0, 0, 0);$$

2) boundary equilibria where only the drug-sensitive strain is present

$$\widetilde{\mathbf{U}} = (\widetilde{S}, \widetilde{I}_1, \widetilde{P}_1, 0, 0);$$

3) boundary equilibria where only the drug-resistant strain is present

$$\bar{\mathbf{U}} = (\bar{S}, 0, 0, \bar{I}_2, \bar{P}_2);$$

4) interior equilibria where both strains are present

$$\widehat{\mathbf{U}} = (\widehat{S}, \widehat{I}_1, \widehat{P}_1, \widehat{I}_2, \widehat{P}_2).$$

Result 3.1. *The parasite-free equilibrium* $\mathbf{U}_0$ *always exists. It is asymptotically stable if* $\mathscr{R}_1 < 1$ *and* $\mathscr{R}_2 < 1$. *It is a saddle if* $\mathscr{R}_1 > 1$ *or* $\mathscr{R}_2 > 1$.

Proof. Introduce the fraction $X = \frac{S}{B+S}$. Then X has a maximum value of one, corresponding to an infinite snail density. X satisfies the equation:

$$\frac{dX}{dt} = rX(1-X) - \frac{1}{B}X(1-X)^2 \sum_{i=1}^{2} \rho_i P_i. \tag{3.1}$$

The Jacobian (with the S equation in (1.3) replaced by the X equation (3.1)) at the equilibrium $(1, 0, 0, 0, 0)$ has one negative eigenvalue, $-r$, and four other eigenvalues, w, given by the equations:

$$w^2 + (u_i + m_i)w + u_i m_i(1 - \mathscr{R}_i) = 0, \quad i = 1, 2.$$

The result follows.

Theorem 3.1 shows that both strains of the parasite will go extinct when their reproductive numbers are below one, while the snail population will grow indefinitely. We do not discuss this equilibrium further since our main concern here is to look at the invasion of resistant strains of the parasites when the sensitive strain is present ($\mathscr{R}_1 > 1$).

There are two possible boundary equilibria of the form $\widetilde{\mathbf{U}}$ at which $S < \infty$ (or $X < 1$). Set the RHS of (1.3) equal to zero and use the fraction $X = S/(B + S)$ to simplify the calculation. Since $\widetilde{I}_2 = \widetilde{P}_2 = 0$ and $\widetilde{P}_1 \neq 0$, we have

$$\widetilde{I}_1 = \frac{\rho_1}{u_1}\widetilde{P}_1\widetilde{X}, \quad \widetilde{P}_1 = \frac{m_1}{\alpha V}(\mathscr{R}_1\widetilde{X} - 1)H, \tag{3.2}$$

and

$$\mathscr{R}_1\widetilde{X}^2 - (\mathscr{R}_1 + 1)\widetilde{X} + (1 + c) = 0,$$

where

$$c = \frac{r\alpha V B}{\rho_1 m_1 H}. \tag{3.3}$$

It is clear that this quadratic equation has two positive solutions given by

$$\widetilde{X}^{\pm} = \frac{\mathscr{R}_1 + 1 \pm \sqrt{(\mathscr{R}_1 - 1)^2 - 4c\mathscr{R}_1}}{2\mathscr{R}_1} \tag{3.4}$$

if

$$(\mathscr{R}_1 - 1)^2 \geq 4c\mathscr{R}_1. \tag{3.5}$$

It is easy to check that $\widetilde{X}^{\pm} < 1$, hence $\widetilde{S}^{\pm} < \infty$. Let $\widetilde{\mathbf{U}}^{\pm}$ denote the equilibria corresponding to $\widetilde{X}^{\pm}$. In order for $\widetilde{\mathbf{U}}^{\pm}$ to exist, we need $\widetilde{P}_1^{\pm}$(given in (3.2)) to be positive. Notice that $\widetilde{X}^{\pm} < 1$ and

$$\begin{aligned}\mathscr{R}_1\widetilde{X}^{\pm} &\geq \frac{1}{2}\left(\mathscr{R}_1 + 1 - \sqrt{(\mathscr{R}_1 - 1)^2 - 4c\mathscr{R}_1}\right)\\ &> 1 \ \text{(if } \mathscr{R}_1 > 1).\end{aligned}$$

It can be shown that $\widetilde{X}^{\pm} > \frac{1}{\mathscr{R}_1}$ if and only if $\mathscr{R}_1 > 1$. Then from (3.2), $\widetilde{P}_1^{\pm} > 0$ if and only if $\mathscr{R}_1 > 1$. Thus we have proved the following result:

Result 3.2. $\widetilde{\mathbf{U}}^{\pm}$ *exist if and only if* $\mathscr{R}_1 > 1$ *and (3.5) holds.*

The condition (3.5) can be easily satisfied when $\mathscr{R}_1 > 1$ and the parameter values of r (the net growth rate of snails) and α are small, in which case c (given in (3.3)) is small. In fact, (3.5) holds for the parameter values used in figure 1. We have already noted that there is also a pseudoequilibrium of the form $\widetilde{\mathbf{U}}$ at which $S = \infty$. We do not discuss it further because in this paper we are not interested in the ability of the parasite to regulate the snail population (Anderson and May, 1979), and we do not suppose that an infinite density approximates a biologically realistic scenario. To the contrary, at many times during the year, snail densities can be quite low and infected snails very rare. At these times, transmission of the parasites from snails to human hosts slows significantly. While we account for the mortality caused by parasites of the two strains on infected snail hosts, this is simply to remove these sources of infection for human hosts at a biologically reasonable rate, and not to suggest that schistosome infection is the major factor regulating the size of snail populations in endemic areas.

The stability of $\widetilde{\mathbf{U}}^{\pm}$ is somewhat difficult to prove. Nevertheless, some analytical insights can be gained by considering the case when the snail population has a very small net growth rate, i.e., $r << 1$.

Result 3.3. *Let* $\mathscr{R}_1 > 1$ *and* $r << 1$. *Then there exists an* $\varepsilon_1 > 0$ *such that* $\widetilde{\mathbf{U}}^{-}$ *is l.a.s. if and only if* $V > \varepsilon_1$ *and*

$$m_1 L(\mathscr{R}_1\widetilde{X}^{-} - 1) > m_2 V(\mathscr{R}_2\widetilde{X}^{-} - 1), \tag{3.6}$$

where $\widetilde{X}^{-}$ *is given in (3.4).* $\widetilde{\mathbf{U}}^{+}$ *is always unstable.*

Proof. As in the proof of Result 3.1, it is convenient to replace the S equation in (1.3) by the X equation (3.1). The Jacobian at $(\widetilde{X}^{\pm}, \widetilde{I}_1^{\pm}, \widetilde{P}_1^{\pm}, 0, 0)$ has the form

$$J = \begin{pmatrix} G_1 & * \\ 0 & G_2 \end{pmatrix},$$

where

$$G_1 = \begin{pmatrix} r\widetilde{X}^{\pm} & 0 & -\frac{r\widetilde{X}^{\pm}(1-\widetilde{X}^{\pm})}{\widetilde{P}_1^{\pm}} \\ \rho_1 \widetilde{P}_1^{\pm} & -u_1 & \rho_1 \widetilde{X}^{\pm} \\ 0 & \lambda_1 H_0 & -m_1 - 2\alpha V \frac{\widetilde{P}_1^{\pm}}{H} \end{pmatrix},$$

$$G_2 = \begin{pmatrix} -u_2 & \rho_2 \widetilde{X}^{\pm} \\ \lambda_2 H_0 & -m_2 - \alpha L \frac{\widetilde{P}_1^{\pm}}{H} \end{pmatrix}.$$

Here we have used the following equivalent expression

$$\frac{\rho_1}{B}\widetilde{X}^{\pm}(1-\widetilde{X}^{\pm})^2 = \frac{r\widetilde{X}^{\pm}(1-\widetilde{X}^{\pm})}{\widetilde{P}_1^{\pm}}.$$

Noticing that

$$\alpha V \frac{P_1^{\pm}}{H} = m_1(\mathscr{R}_1 \widetilde{X}^{\pm} - 1),$$

we obtain the characteristic equation of G_1:

$$\|J(G_1) - \omega I\| = \omega^3 + C_0\omega^2 + C_1\omega + C_2 = 0,$$

where

$$\begin{aligned} C_0 &= u_1 + m_1 + 2m_1(\mathscr{R}_1\widetilde{X}^{\pm} - 1) - r\widetilde{X}^{\pm}, \\ C_1 &= u_1 m_1(\mathscr{R}_1\widetilde{X}^{\pm} - 1) - r(u_1 + m_1)\widetilde{X}^{\pm} - 2rm_1\widetilde{X}^{\pm}(\mathscr{R}_1\widetilde{X}^{\pm} - 1), \\ C_2 &= ru_1m_1\widetilde{X}^{\pm}(\mathscr{R}_1 + 1 - 2\mathscr{R}_1\widetilde{X}^{\pm}). \end{aligned}$$

From (3.4), $\mathscr{R}_1 + 1 - 2\mathscr{R}_1\widetilde{X}^{+} = -\sqrt{(\mathscr{R}_1 - 1)^2 - 4c\mathscr{R}_1} < 0$, which gives that $C_2 < 0$ at $\widetilde{\mathbf{U}}^{+}$. It follows from the Routh-Hurwitz criterion that G_1 has an eigenvalue with positive real part. Hence, $\widetilde{\mathbf{U}}^{+}$ is unstable. At $\widetilde{\mathbf{U}}^{-}$, we can show that $C_0 > 0$, $C_2 > 0$ for small r. Let

$$\varepsilon_1 = \frac{\rho_1 H}{\alpha u_1 B}\left(1 - \frac{1}{\mathscr{R}_1}\right)\left(\frac{u_1 m_1}{u_1 + m_1}(1 - \frac{1}{\mathscr{R}_1}) + \frac{u_1 + m_1}{\mathscr{R}_1}\right).$$

Then, after some algebra, we get that $C_0C_1 > C_2$ if and only if $V > \varepsilon_1$. Using the Routh-Hurwitz criterion again, we know that all the eigenvalues of G_1 have negative real parts. Direct calculations show that G_2 has two eigenvalues with negative real part if (3.6) holds, and one positive eigenvalue if (3.6) is reversed.

This finishes the proof.

Although the condition $V > \varepsilon_1$ is hard to interpret, this condition is satisfied when the scaling constant B is large and the parasites are highly aggregated within the human hosts, i.e., V is large, which has been observed for many macroparasite infections.

Using the symmetry between the equations for P_1 and P_2 we can obtain similar conditions for the stability of the boundary equilibrium $\bar{\mathbf{U}}^{-}$: (i) $V > \varepsilon_2$, where ε_2 has the same formula as ε_1 with the subscript 1 replaced by 2, and (ii)

$$m_2 L(\mathscr{R}_2\bar{X}^{-} - 1) > m_1 V(\mathscr{R}_1\bar{X}^{-} - 1). \tag{3.7}$$

Coexistence is expected when both $\widetilde{\mathbf{U}}^-$ and $\bar{\mathbf{U}}^-$ are unstable. If there is no treatment, i.e., $\sigma = 0$, then $m_1 = m_2$. It is easy to show that (3.6) holds if and only if $\mathscr{R}_1 > \mathscr{R}_2$, and (3.7) holds if and only if $\mathscr{R}_1 < \mathscr{R}_2$. Hence coexistence can only occur on the line $\mathscr{R}_1 = \mathscr{R}_2$. If, however, the drug treatment rate σ is not zero and the parasites are paying a cost for drug resistance, then $m_1 > m_2$ and $\mathscr{R}_i$, $\widetilde{X}^-$, $\bar{X}^-$ are all functions of σ and θ_i. Using θ for θ_2, $\theta_1 = 1$, we can rewrite (3.6) and (3.7) as $F_1(\sigma, \theta) > 0$ and $F_2(\sigma, \theta) > 0$, respectively, where

$$\begin{aligned} F_1(\sigma, \theta) &= m_1 L(\mathscr{R}_1 \widetilde{X}^- - 1) - m_2 V(\mathscr{R}_2 \widetilde{X}^- - 1), \\ F_2(\sigma, \theta) &= m_2 L(\mathscr{R}_2 \bar{X}^- - 1) - m_1 V(\mathscr{R}_1 \bar{X}^- - 1). \end{aligned} \tag{3.8}$$

The plots of the two functions F_1 and F_2 are shown in figure 2 (on the left) and the coexistence region

$$\Omega = \left\{(\sigma, \theta) \mid F_i(\sigma, \theta) < 0,\ i = 1, 2\right\}$$

is shown by the contour plot in figure 2 (on the right). l_i represents the curve on which $F_i(\sigma, \theta) = 0$. The parameter values used for figure 2 are the same as for figure 1. We can show that, for $(\sigma, \theta) \in \Omega$, there are two interior equilibria $\widehat{U}^{\pm}$.

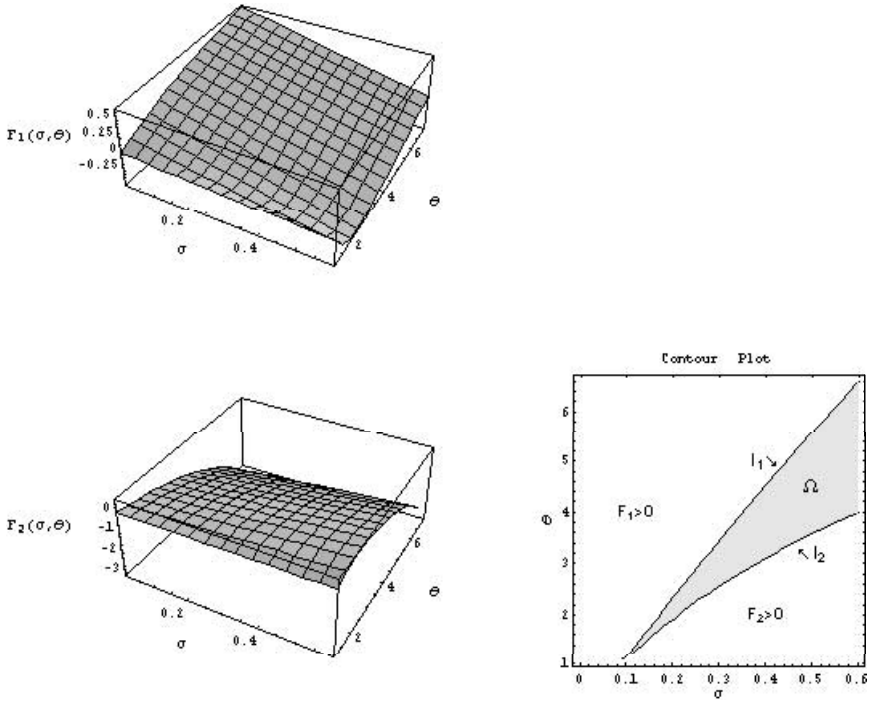

Fig. 2. Bifurcation diagrams on the (σ, θ) plane. $\widetilde{U}^-$ is stable when $F_1(\sigma, \theta) > 0$, $\bar{U}^-$ is stable when $F_2(\sigma, \theta) > 0$, and $\widehat{U}^-$ is stable when $F_i(\sigma, \theta) < 0$, $i = 1, 2$, i.e., $(\sigma, \theta) \in \Omega$ (the shaded area).

Our numerical computations shown in figure 3 support the same bifurcation diagram described in figure 2 and indicate that $\widehat{U}^-$ is stable. The parameters have the same values as that used for figure 2 and $\sigma = 0.4$. For this value of σ, $F_1(0.4, \theta) = 0$ at $\theta = 4.55$. In figure 3(a), $\theta = 4.65$ is chosen such that (σ, θ) is slightly above the curve l_1 and hence $\widetilde{U}^-$ is stable. In figure 3(b), $\theta = 4.5$ such that (σ, θ) is slightly below the curve l_1 and belongs to Ω, and hence $\widetilde{U}^-$ is unstable and solutions converge to the coexistence equilibrium $\widehat{U}^-$. It also shows that coexistence cannot occur if the treatment rate σ is small and close to zero. Hence, the following result has been established:

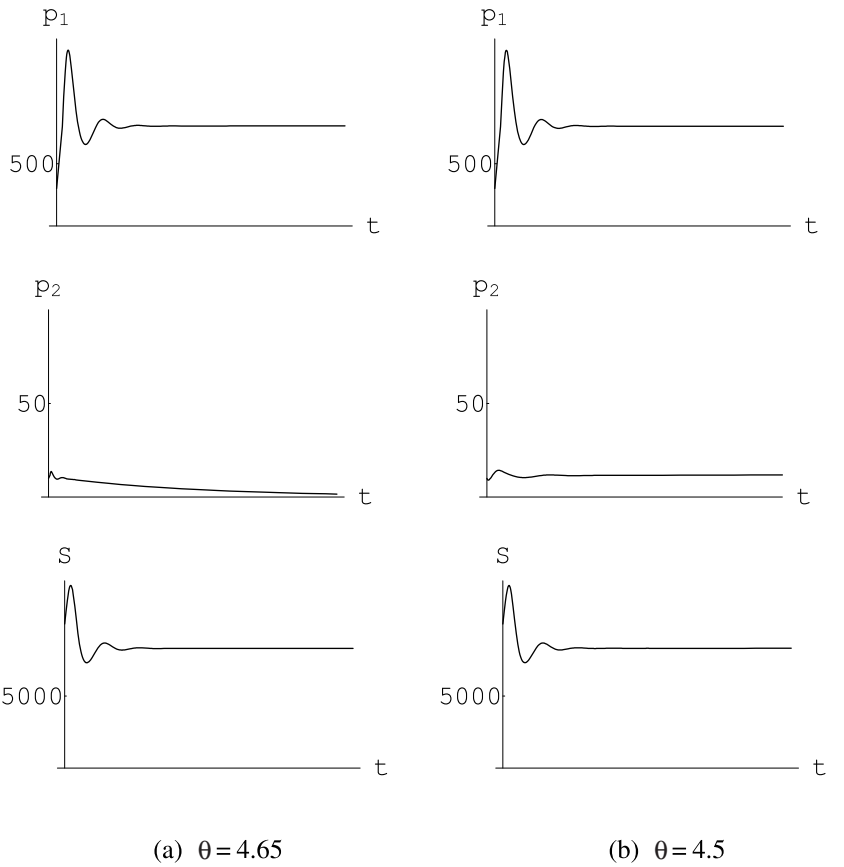

Fig. 3. Plots of number of parasites P_i $(i = 1, 2)$ and uninfected snails S vs. time for two sets of $\mathscr{R}_i$ values (using the system (1.3)). The parameter values are the same as for Fig. 2, and $\sigma = 0.4$. For this set of values, $F_1 = 0$ at $\theta = 4.55$. Fig. 3(a) shows that when (σ, θ) is slightly above l_1 ($\theta = 4.65 > 4.55$), the resistant strain P_2 become extinct (stability of $\widetilde{\mathbf{U}}^-$). Fig. 3(b) shows that when (σ, θ) is slightly below l_1 and belongs to Ω ($\theta = 4.5 < 4.55$), the resistant strain, P_2, coexists with the susceptible strain, P_1 (stability of $\widehat{\mathbf{U}}^-$).

Result 3.4. *Let $L = V$. (a) If there is no drug treatment ($\sigma = 0$), then the two strains of parasites cannot coexist whenever $\mathscr{R}_2 \neq \mathscr{R}_1$. (b) If $\sigma > 0$, then coexistence occurs for treatment rates and resistance levels in a well defined region Ω.*

As mentioned in the Introduction, our numerical studies of this case indicate that drug resistance of the parasites and the associated cost in parasite reproduction may indeed provide a mechanism for coexistence. Since we are interested in the increase in frequency of resistant individuals (regardless of whether or not the sensitive strain becomes extinct), we consider the conditions under which this increase occurs to be equivalent to the conditions under which the resistance-free equilibrium becomes unstable. That is, the instability of $\widetilde{U}^-$ implies that parasite strains with some level of resistance have invaded the population. Thus, the condition $F_1(\sigma, \theta) < 0$ provides an invasion criterion and can be used to determine the impact of drug treatment on the increase of resistant strains. For simplicity we demonstrate our analytical result using an approximate formula instead of the original inequality $F_1(\sigma, \theta) < 0$. Under the assumption of r being small, we can write $\widetilde{X}^-$ in expansion of r:

$$\widetilde{X}^- = \frac{1}{\mathscr{R}_1} + \frac{\alpha V B}{m_1 \rho_1 (\mathscr{R}_1 - 1) H} r + O(r^2).$$

Then

$$\begin{aligned} F_1(\sigma, \theta) &= m_1 L\big(\mathscr{R}_1 \widetilde{X}^- - 1\big) - m_2 V\big(\mathscr{R}_2 \widetilde{X}^- - 1\big) \\ &= V m_2 \left(1 - \frac{\mathscr{R}_2}{\mathscr{R}_1} + \frac{\alpha B\big(m_1 L \mathscr{R}_1 - m_2 V \mathscr{R}_2\big) r}{m_1 m_2 \rho_1 (\mathscr{R}_1 - 1) H} + O(r^2)\right). \end{aligned}$$

Hence

$$F_1(\sigma, \theta) < 0 \quad \Longleftrightarrow \quad \mathscr{R}_2 > b \mathscr{R}_1, \tag{3.9}$$

where

$$b = 1 + O(r).$$

We will use (3.9) as a condition for the invasion of resistant strains.

Result 3.5. *Higher treatment rate can lead to coexistence between a number of different parasite strains with a larger range of resistance levels.*

Proof. Using (2.1) and (2.2), we can rewrite the reproductive number $\mathscr{R}_2$ as a function of resistance level θ:

$$\mathscr{R}_2(\theta) = \frac{\lambda_1 \rho_1 H_0 \theta}{\Big((\mu_h + \mu + \alpha)\theta + \sigma\Big)\Big(\phi \nu \theta + \delta_1\Big)}.$$

Here we again used the notation θ for θ_2 and $\theta_1 = 1$. We observe that $\mathscr{R}_2(1) = \mathscr{R}_1$ and that $\mathscr{R}_2(\theta)$ has a unique maximum (see figure 4) at the critical point

$$\theta_c = \sqrt{\left(\frac{\sigma}{\mu_h + \mu + \alpha}\right)\left(\frac{\delta_1}{\phi \nu}\right)}.$$

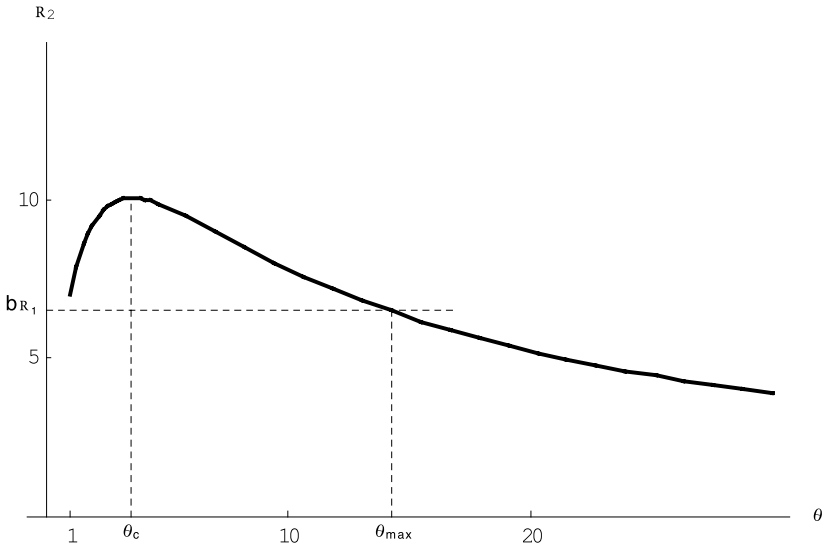

Fig. 4. A curve of the reproductive number $\mathscr{R}_2$ as a function of resistance level $\theta_2 = \theta$. The parameter values are the same as for Fig. 2 except that $\sigma = 0.5$. $b\mathscr{R}_1$ ($\mathscr{R}_1 = 7$) is marked on the $\mathscr{R}_2$ axis. Note that $\theta = 3.5$ is the critical point θ_c at which $\mathscr{R}_2$ assumes its maximum value 10.1, making strains with this resistance level the most competitive under the given conditions. In the interval $(1, \theta_{\max})$, $\mathscr{R}_2 > b\mathscr{R}_1$, which is a necessary condition for the resistant strain to invade and persist in the parasite population. When $\theta > \theta_{\max}$, the boundary equilibrium $\widehat{\mathbf{U}}^-$ is stable, and the resistant strain cannot persist due to the competition with the susceptible strain.

Since $\theta > 1$, we are only interested in values of σ large enough so that $\theta_c > 1$. Let

$$\theta^* = \theta_c^2 = \left(\frac{\sigma}{\mu_h + \mu + \alpha}\right)\left(\frac{\delta_1}{\phi\nu}\right).$$

Then it can be checked that $\mathscr{R}_2(\theta^*) = \mathscr{R}_1$ and $\theta^* > 1$. Noticing that $\mathscr{R}_2(\theta)$ decreases for $\theta > \theta_c$, we know that $\mathscr{R}_2(\theta) > \mathscr{R}_1$ for all $\theta < \theta^*$ and that $\mathscr{R}_2(\theta) < \mathscr{R}_1$ for all $\theta > \theta^*$. Since $b = 1 + O(r)$, there exists a $\theta_{\max} = \theta^* + O(r)$ such that (see figure 4)

$$\begin{aligned} \mathscr{R}_2(\theta) &> b\mathscr{R}_1 \qquad \text{for all } 1 < \theta < \theta_{\max}, \\ \mathscr{R}_2(\theta) &< b\mathscr{R}_1 \qquad \text{for all } \theta > \theta_{\max}. \end{aligned}$$

It follows from (3.9) that $\theta_{\max}$ is the maximum level of resistance that can be maintained in an equilibrium distribution. Notice that $\theta_{\max}$ decreases with decreasing treatment rate σ. Thus, the higher the treatment rate is, the larger range of resistance values there will be for a resistant strain to occupy while maintaining the possibility for coexistence. However, for a fixed treatment rate, any strain with resistant level higher than $\theta_{\max}$ will become extinct. Also, if the treatment rate is too low, i.e., σ

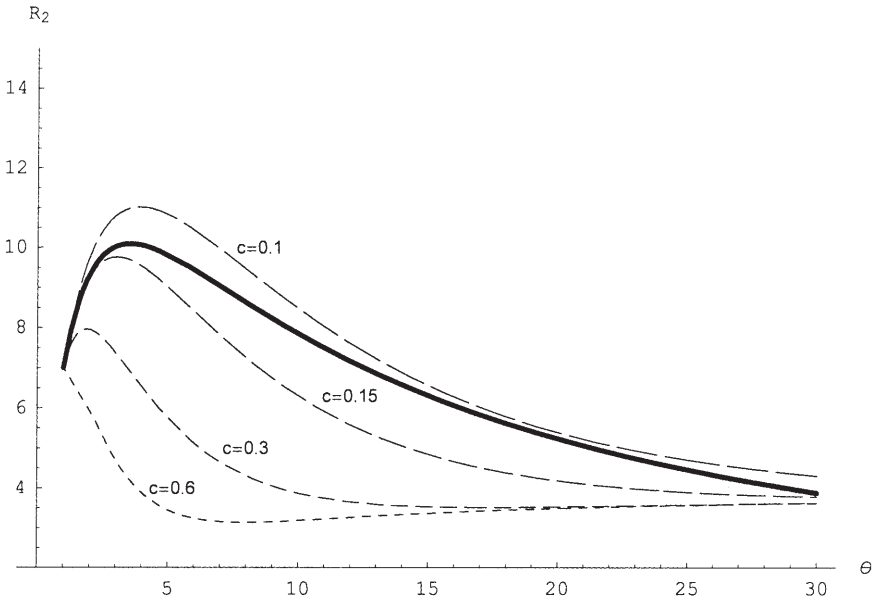

Fig. 5. Comparison of curves of $\mathscr{R}_2$ vs. the resistance level $\theta_2 = \theta$ for various cost functions. The solid curve is for the functions given in (2.1) and the dashed curves are for (3.10) with various values of c. The parameter values are the same as for Fig. 4, and $\lambda_0 = 20$, $\rho_0 = 1$, $\delta_0 = 0.4$.

is small such that $\theta_c < 1$, then the resistant strain will not be able to invade. The result follows.

Result 3.4 is shown for the particular form of the cost of resistance given in (2.1). We have also considered several forms different than (2.1). For example, the following form

$$\lambda_i \rho_i = \lambda_1 \rho_1 e^{0.3(1-\theta_i)}, \quad \delta_i = \delta_1 e^{0.3(1-\theta_i)}, \quad i = 2, 3, \cdots, n$$

produces results that are qualitatively similar to that of (2.1). A more realistic cost-of-resistance relationship perhaps needs to assume that the parasite reproduction rates saturate at a minimum value for high levels of resistance. One of the choices of such cost functions could be

$$\omega_i = (\omega_1 - \omega_0) e^{c(1-\theta_i)} + \omega_0, \quad \omega = \lambda,\ \rho,\ \delta \tag{3.10}$$

where ω_0 is the saturation constant and c is a measure for the level of cost. The corresponding reproductive number, $\mathscr{R}_i$, as a function of the resistance level θ_i, has similar properties as in the case when (2.1) is used (see figure 5 for $i = 2$). For figure 5, all the parameter values are chosen to be the same as in figure 4, and $\lambda_0 = 20$, $\rho_0 = 1$, $\delta_0 = 0.4$, $\theta_2 = \theta$, $\theta_1 = 1$. We see that $\mathscr{R}_2(\theta) < \mathscr{R}_2(1) = \mathscr{R}_1$ for all $\theta > 1$ when c is large (higher level of cost). In this case, the resistant strains are not able to invade. When c is small, there exists a $\theta_{\max}$ such that $\mathscr{R}_2(\theta) > b\mathscr{R}_1$ for $1 < \theta < \theta_{\max}$ and $\mathscr{R}_2(\theta) > b\mathscr{R}_1$ for $\theta > \theta_{\max}$.

4. Discussion

We have formulated a model for schistosomiasis incorporating intermediate snail hosts, drug-treatment of humans, and parasite resistance to the drug. We have exhibited the basic reproductive number $\mathscr{R}_i$ for each strain in the case of two parasite strains, studied the asymptotical stability of the steady states, and demonstrated the impact of drug treatment on the coexistence of multiple parasite strains. We have applied our theoretical findings to the biological questions proposed in the Introduction.

The results presented in this paper have implications for both the effects of drug treatment on parasite genetic diversity, and the selection for drug resistance of parasites that utilize both definitive hosts and intermediate hosts. The results show that increasing treatment rate can lead to a polymorphism of parasite strains with many different levels of resistance within a well defined range, and that when the treatment rate is very low, resistance is not selected for. The intuitive reason for this is that if the cost of resistance in the parasite is high, one would not expect resistance when there is little selection pressure from the drugs. Other non-resistant strains would outcompete it under these conditions. Resistant strains can only increase in frequency (and potentially, in number) when the selection pressure (treatment rate) is high. Mathematically, increasing the value of σ results in: 1) a reduction in the basic reproductive number $\mathscr{R}_1$ of the non-resistant strain; and, 2) an increase in the range of resistance levels θ_i for which $\mathscr{R}_i > b\mathscr{R}_1$. These are strains that are able to invade a host population. On the other hand, if σ is small such that $\theta_{\max}$ is close to one, then $\mathscr{R}_i < b\mathscr{R}_1$ for most levels of resistance θ_i. These strains will not be maintained in a population. Both numerically and analytically, we have demonstrated coexistence of parasite strains with varying levels of resistance.

Herein, we have attempted to model the conditions that favor a parasite population with a polymorphism for drug resistance. Our analysis has taken the form of considering the ability of resistant strains to invade/coexist in a population composed mainly of susceptible individuals. One major limitation of this model's ability to predict outcomes arises in the mating biology of the parasites. Schistosomes have separate sexes that mate (presumably, for life) within the human hosts. It would be mathematically very difficult to incorporate interstrain mating into this model. For example, for the population shown in figure 1 ($i = 4$), there are six different interstrain mating combinations possible (disregarding which strain represents the male and female worm). It is unclear what the resistance level of the offspring worms would be. Should their θ be an average of the values from their mother and father? In reality, each interstrain mating event could conceivably create another novel strain. Furthermore, when a pair of worms representing an interstrain mating is exposed to PZQ, which worm's resistance determines whether the pair survives? Questions such as these indicate an area of schistosome modeling that may be more readily addressed through simulation than deterministic methods, and we have begun working to this end.

These results demonstrate that the level of drug treatment of patients in the human population helps to determine whether a parasite strain with a certain resistance level is able to invade and persist in the parasite population. The work described

in this paper also suggests that low levels of resistance will be maintained by the various strains in the parasite population; the extent to which parasites will do so depends on the degree to which transmission rates are linked with the cost of resistance. There is, however, a great need for data directed towards these issues. Thus, although we have shown how treatment can lead to an increase in parasite genetic diversity, the extent to which it does so in natural populations is unclear.

Acknowledgements. We thank Simon Levin and Andy Dobson for useful discussions, and Fabio Milner, Jonathan Dushoff, and an anonymous reviewer for helpful suggestions. This work was carried out while Zhilan Feng was visiting the Department of Ecology and Evolutionary Biology at Princeton University with NSF support DMS-9720558. The work is also supported by both the National Institutes of Health (R01-AI 42768) and by the National Science Foundation (DMS-9974389).

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