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On the role of schistosome mating structure in the maintenance of drug resistant strains

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Abstract

The effects of drug treatment of human hosts upon a population of schistosome parasites depend upon a variety of factors. Previous models have shown that multiple strains of drug-resistant parasites are likely to be favored as the treatment rate increases. However, such models have neglected to account for the complex nature of schistosome mating biology. To more accurately account for the biology of these parasites, a simple mating structure is included in a multi-strain schistosome model, with parasites under the influence of drug treatment of their human hosts. Parasites are assumed to pay a cost for drug resistance in terms of reduced reproduction and transmission. The dynamics of the parasite population are described by a system of homogeneous differential equations, and the existence and stability of the exponential solutions for this system are used to infer the impact of drug treatment on the maintenance of schistosome genetic diversity.

1. Introduction

Schistosomiasis is a major parasitic disease infecting 200 million people in Africa, Asia, and South America (Chitsulo et al., 2000; WHO, 2004). Currently, the most efficient

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method of schistosomiasis control involves chemotherapeutic treatment of patients with praziquantel (PZQ) (Fenwick et al., 2003). This drug kills the adult worms residing within the patient, effectively halting the deposition of parasite eggs within host tissues, and preventing the further worsening of symptoms. However, reports suggest that schistosome populations in some endemic areas may be developing resistance to PZQ (Ismail et al., 1999). Thus, disease control programs employing chemotherapeutic agents may select for varying degrees of drug resistance in parasite populations (at different spatial and temporal scales). If a natural schistosome population consists of a collection of "strains" that express different levels of resistance, then it will be important to understand the consequences of this genetic diversity on both disease transmission and proposed disease control strategies.

Previously, we have studied schistosomiasis models which consider both human and snail hosts as well as other detailed biology such as infection age of snails and density-dependent recruitment rates (Feng et al., 2001, 2002). For example, in Feng et al. (2001), we proposed a mathematical model that attempted to incorporate parasite resistance to chemotherapy. The model envisioned a number of parasite strains, each defined by its inherent resistance to the treatment drug. Parasite strains paid a cost in diminished reproduction and transmission that was inversely related to the level of drug resistance, because without such costs, the most resistant strain would be expected to dominate the population very quickly, even if treatment occurred at a very low rate. We showed that as drug treatment of the population of human patients increased, a greater number of resistant parasite strains (with higher levels of resistance) were able to coexist, and that a fully susceptible strain would go locally extinct.

A recognized limitation of our earlier models arose from the fact that schistosomes have separate sexes, and thus, the reproduction of the different strains was likely to be much more complex (in terms of mathematical logistics and the underlying biology) than we were able to model with that system of equations. By accounting for the separate male and female worms of each strain, we have attempted to create a more robust model of the spread of drug resistance in schistosome populations. This model retains the assumption of a simple genetic basis for resistance, as we employed in our earlier model, but now allows for mating between individuals of two different strains. We make the further assumption that the offspring of such inter-strain matings will have the same values for drug resistance as their parents (i.e., intermediate values of resistance, potentially corresponding to new strains, are not generated). Incorporating this important feature of schistosome mating biology greatly complicates the model—as we now have equations for unmated male worms and unmated female worms of each strain, along with an equation for each possible strain combination as a mated pair—and yet, the results of our analysis are qualitatively very similar to those obtained with our previous model. Thus, the treatment rate affects the range of resistance values (e.g., variety of strains) that can coexist in the parasite population, and if high enough, may lead to the exclusion of susceptible strains. Furthermore, it is possible to calculate a treatment rate below which resistant strains cannot invade a population of mostly susceptible parasites, although this "critical rate" depends upon the reproductive costs that parasites pay for resistance.

When two strains (drug-sensitive and -resistant strains) are considered, our model is an eight-dimensional system of homogeneous equations of degree one. Following the approach of Hadeler and co-workers (see Hadeler et al., 1988; Hadeler, 1989; Hadeler and Ngoma, 1990) we studied both analytically and numerically the existence and stability of exponential solutions of the system. Our bifurcation analysis provides threshold conditions which can be used to determine whether the resistant strain can invade a population consisting of only the sensitive strain of parasites. Results for the two-strain model are extended numerically to cases when more than two strains are considered. This paper is organized as follows. In Section 2 we consider a simple one-strain model and study persistent proportions of populations represented by exponential solutions of the model. The results in this section will be applied to the study of the two-strain model described in Section 3. Existence and stability of exponential solutions of the full system are also given in Section 3. Section 4 is devoted to numerical simulations to confirm or extend the analytic results.

2. The model for a single strain of schistosomes

In this section we consider a one-strain model for a population of schistosome parasites whose human hosts are treated with chemotherapy. This schistosome population is divided into three subpopulations: f and m are the densities of female and male singles, respectively, and p is the density of pairs. The formation of schistosome pairs is described by a "mating function", $\varphi : \mathbb{R}^2_+ \to \mathbb{R}_+$, satisfying

(i) Preservation of positivity: $\varphi(m, 0) = \varphi(0, f) = 0$;
(ii) Homogeneity: $\varphi(\alpha m, \alpha f) = \alpha\varphi(m, f), \forall \alpha > 0$;
(iii) Monotonicity: $\varphi(m + u, f + v) \geq \varphi(m, f)$ for all $u, v \geq 0$.

Let b be the per capita birth rate of a pair, and let μ_s and μ_p be the per capita death rates of single worms and worms in a mated pair, respectively. Note that we assume that both members of a mated pair are killed simultaneously; individuals in the model do not lose their mate and return to the population of single worms. A disease control program distributes a chemotherapeutic drug to the host population at a constant rate, but the effectiveness of the drug in killing individuals of a particular strain of schistosomes is reduced by a factor, θ, which we call the "drug resistance" of that parasite strain. $\theta > 1$ means that the strain of schistosomes has some degree of resistance to the drug, while $\theta = 1$ implies the strain is entirely sensitive to the drug. Thus, due to drug treatment of their hosts, a fully sensitive strain of parasites has a per capita death rate, σ, and this death rate is reduced by the factor $\theta > 1$, σ/θ, for strains with innate drug resistance. Then, the model for schistosomes is given by

$$\begin{aligned} \dot{m} &= kp - \left(\mu_s + \frac{\sigma}{\theta}\right) m - \varphi(m, f), \\ \dot{f} &= kp - \left(\mu_s + \frac{\sigma}{\theta}\right) f - \varphi(m, f), \\ \dot{p} &= \varphi(m, f) - \left(\mu_p + \frac{\sigma}{\theta}\right) p, \end{aligned} \tag{2.1}$$

where $k = b/2$, i.e., the ratio of female to male offspring is assumed to be 1:1 (Gryseels and de Vlas, 1996). Following the approach of Pollard (1973) we assume that the mating function φ takes the form of $\frac{2\rho mf}{m+f}$, where 2ρ represents the effective contact number (which may be a product of several parameters including the average contact number of a parasite and the probability of a pair being formed per contact). Other forms of mating functions can also be considered (see for example Castillo-Chavez et al. (1996, 1999), Hadeler et al. (1988), Hadeler (1989), Hadeler and Ngoma (1990) and Pollard (1973)).

For system (2.1), stationary solutions can not be expected due to the homogeneity. Instead, we can look for persistent distributions, i.e., exponential solutions of the form

$$(m(t),\ f(t),\ p(t)) = (\bar{m},\ \bar{f},\ \bar{p})\mathrm{e}^{\lambda t}, \tag{2.2}$$

where $\bar{m},\ \bar{f},\ \bar{p}$ are constants. Hadeler et al. (Hadeler et al., 1988; Hadeler, 1989; Hadeler and Ngoma, 1990) provided a systematic approach to the existence and stability of exponential solutions for homogeneous evolution equations, which proceeds as follows. Consider a population model

$$\dot{x}(t) = f(x(t)), \tag{2.3}$$

where the function f is continuously differentiable on $\mathbb{R}^n_+ \setminus \{0\}$, and homogeneous, i.e., $f(\alpha x) = \alpha f(x)$ for all $\alpha, x > 0$. We require that zero is a stationary point of (2.3), and that the first quadrant $\mathbb{R}^n_+$ is invariant for the solution semiflow of Eq. (2.3). Let

$$y = \frac{x}{e^* \cdot x} \qquad \text{for } x \in \mathbb{R}^n_+ \setminus \{0\},$$

where the dot "$\cdot$" denotes the inner product on $\mathbb{R}^n$, $e^* = (1, 1, \ldots, 1)$. That is, the variable vector y is the proportion vector of x to the total population. Then, the proportion variable y satisfies

$$\dot{y}(t) = f(y(t)) - e^* \cdot f(y(t))y(t) \tag{2.4}$$

on the simplex $S = \{y \geq 0 : e^* \cdot y = 1\}$. A solution $y(t)$ of (2.4) corresponds to the following group of solutions to (2.3):

$$x(t) = y(t)\mathrm{e}^{\int_0^t e^* \cdot f(y(s))\mathrm{d}s} e^* \cdot x(0).$$

If $\bar{y} \in S$ is an equilibrium of (2.4), then the corresponding solutions of (2.3) are of the form

$$x(t) = \bar{y}\mathrm{e}^{\bar{\lambda}t} e^* \cdot x(0),$$

where $\bar{\lambda} = e^* \cdot f(\bar{y})$. If $\bar{y}$ is globally asymptotically stable, then a subset of the population may increase or decrease over time, but always represents the same proportion of the total population. Thus, the existence and stability of equilibria of (2.4) are important issues. Fortunately, Hadeler et al. (1988) provided a simple result: if we denote the eigenvalues of the Jacobian $f'(\bar{y})$ by $\lambda_1 = \bar{\lambda}, \lambda_2, \ldots, \lambda_n$ (multiplicities counted), then $\bar{y}$ is linearly stable if all of the real parts of the numbers $\lambda_i - \bar{\lambda}$, $i = 2, 3, \ldots, n$, are less than zero.

Using the above approach, we will discuss the stability of the exponential solutions for the two models in this paper. In the following, we say that an exponential solution $\bar{y}e^{\bar{\lambda}t}$ of a system is trajectorally stable (or simply stable), if the equilibrium $\bar{y}$ is stable with respect to the corresponding proportion system (2.4).

Substituting (2.2) into system (2.1), we have

$$\begin{aligned} k\bar{p} - \left(\mu_s + \frac{\sigma}{\theta}\right)\bar{m} - \varphi(\bar{m}, \bar{f}) &= \lambda\bar{m}, \\ k\bar{p} - \left(\mu_s + \frac{\sigma}{\theta}\right)\bar{f} - \varphi(\bar{m}, \bar{f}) &= \lambda\bar{f}, \\ \varphi(\bar{m}, \bar{f}) - \left(\mu_p + \frac{\sigma}{\theta}\right)\bar{p} &= \lambda\bar{p}. \end{aligned}$$

There are two trivial solutions (up to a constant)

$$E_m = (1, 0, 0) \qquad \text{and} \qquad E_f = (0, 1, 0) \qquad \text{with } \lambda_{m,f} = -\mu_s - \frac{\sigma}{\theta}, \tag{2.5}$$

and a unique positive solution E_p with λ_p, where

$$\begin{aligned} E_p &= (1, 1, \bar{p}) = \left(1, 1, \frac{\rho}{\lambda_p + \mu_p + \frac{\sigma}{\theta}}\right), \\ \lambda_p &= -\frac{1}{2}\left(\mu_s + \mu_p + \rho + \frac{2\sigma}{\theta}\right) + \frac{1}{2}\sqrt{(\mu_s - \mu_p + \rho)^2 + 4k\rho}. \end{aligned}$$

To study the stability of exponential solutions, we need to check the eigenvalues of the corresponding Jacobian matrices of system (2.1). The Jacobian at E_m can be readily obtained:

$$J_m = \begin{pmatrix} -\mu_s - \frac{\sigma}{\theta} & * \\ 0 & C_m \end{pmatrix}, \qquad C_m = \begin{pmatrix} -\mu_s - \frac{\sigma}{\theta} - 2\rho & k \\ 2\rho & -\mu_p - \frac{\sigma}{\theta} \end{pmatrix}.$$

Here, the matrix block denoted by $*$ is not of interest. Then, $E_m e^{\lambda_{m,f}t}$ is trajectorally stable if $\lambda_{m,f} > \lambda_{C_m}$, where λ_{C_m} is the dominant eigenvalue of C_m. It is easy to get that

$$\lambda_{C_m} = -\frac{1}{2}\left(\mu_s + \mu_p + 2\rho + \frac{2\sigma}{\theta}\right) + \frac{1}{2}\sqrt{(\mu_s - \mu_p + 2\rho)^2 + 8k\rho}.$$

Therefore, $E_m e^{\lambda_{m,f}t}$ is trajectorally stable if and only if $\mu_p - \mu_s + 2\rho > 0 > \mu_s - \mu_p + k$. A similar computation shows that $E_f e^{\lambda_{m,f}t}$ is trajectorally stable if and only if the same conditions hold.

To investigate the stability of the positive exponential solution $E_p e^{\lambda_p t}$, we reduce system (2.1) to a two-dimensional system by introducing projective variables

$$\xi = \frac{m}{p}, \qquad \eta = \frac{f}{p}.$$

The new system is given by

$$\begin{aligned}\dot{\xi} &= k - (\mu_s - \mu_p)\xi - \frac{2\rho\xi\eta}{\xi+\eta}(1+\xi),\\ \dot{\eta} &= k - (\mu_s - \mu_p)\eta - \frac{2\rho\xi\eta}{\xi+\eta}(1+\eta).\end{aligned} \tag{2.6}$$

For this system, $\mathbb{R}^2_+$ is strictly positive invariant. Moreover, this system is an irreducible and competitive system. At $(\bar{\xi},\bar{\eta}) = (1/\bar{p}, 1/\bar{p})$, the Jacobian of the right-hand side of (2.6) is

$$\begin{aligned} J_p &= \begin{pmatrix} -\mu_s+\mu_p-\frac{\rho}{\bar{p}}-\frac{1}{2}\rho\left(1+\frac{1}{\bar{p}}\right) & -\frac{1}{2}\rho\left(1+\frac{1}{\bar{p}}\right) \\ -\frac{1}{2}\rho\left(1+\frac{1}{\bar{p}}\right) & -\mu_s+\mu_p-\frac{\rho}{\bar{p}}-\frac{1}{2}\rho\left(1+\frac{1}{\bar{p}}\right) \end{pmatrix} \\ &= \begin{pmatrix} -\mu_s-\frac{3}{2}\lambda_p-\frac{3}{2}\frac{\sigma}{\theta}-\frac{1}{2}\mu_p-\frac{1}{2}\rho & -\frac{1}{2}\left(\rho+\lambda_p+\mu_p+\frac{\sigma}{\theta}\right) \\ -\frac{1}{2}\left(\rho+\lambda_p+\mu_p+\frac{\sigma}{\theta}\right) & -\mu_s-\frac{3}{2}\lambda_p-\frac{3}{2}\frac{\sigma}{\theta}-\frac{1}{2}\mu_p-\frac{1}{2}\rho \end{pmatrix}. \end{aligned}$$

We can show that the maximum eigenvalue of J_p is $-\lambda_p - \mu_s - \frac{\sigma}{\theta}$. Therefore, $(\bar{\xi},\bar{\eta})$ is stable if $\lambda_p+\mu_s+\frac{\sigma}{\theta} > 0$, i.e., $\mu_p-\mu_s+\rho < 0$ or $\mu_s-\mu_p+k > 0$. Moreover, if it is stable, then it is globally asymptotically stable because of the monotonicity and dissipativity of the solution semiflow associated with (2.6).

Collecting the results on the stability of exponential solutions, we have

Theorem 2.1. *The trivial exponential solutions $E_m e^{\lambda_{m,f}t}$ and $E_f e^{\lambda_{m,f}t}$ are locally trajectorally stable if and only if $\mu_s-\mu_p+k < 0 < \mu_p-\mu_s+2\rho$. The persistent solution $E_p e^{\lambda_p t}$ is globally trajectorally stable if and only if $\mu_s-\mu_p+k > 0$, or $\mu_p-\mu_s+\rho < 0$.*

In reality, pairs of schistosomes may live for a few years while single parasites may only live for a few weeks. Therefore, in this paper, we always assume that the death rate of pairs should be less than that of singles, i.e., $\mu_p < \mu_s$. Under this condition, the two trivial exponential solutions can not be stable and the persistent solution is stable. We also have the following observations:

(1) The treatment rate σ, and drug resistance θ, have no effects on the stability of the exponential solutions, particularly the persistent solution $E_p e^{\lambda_p t}$, which shows constant proportions of male and female singles and of pairs.
(2) If $\lambda_p > 0$, the whole population of schistosomes is increasing, whereas if $\lambda_p < 0$, the whole population is decreasing. Thus, the exponent λ_p can be regarded as a reproduction rate for this particular strain of schistosomes.
(3) The treatment rate, σ, and the degree of resistance, θ, affect the sign of λ_p. An increase in the treatment rate, σ, reduces the growth rate, λ_p, of the population, while an increase in θ leads to an increase in λ_p.

The stability results obtained in this section will be used in Section 3 for the two-strain model.

3. The model for two strains of schistosomes

We assume that the whole schistosome population consists of individuals belonging to one of two strains with different levels of drug resistance, θ. (In the following, let $\theta_1 < \theta_2$.) The following definitions are required for the formulation of the model:

m_i = density of single males of strain i,
f_i = density of single females of strain i,
p_{ij} = density of pairs with strain i male and strain j female,
φ_{ij} = the mating function of strain i male and strain j female.

In order to model the heredity of drug resistance, it is further assumed that the offspring of an interstrain mating inherit either the paternal or maternal drug resistance with equal frequency, and that pairs produce equal numbers of male and female offspring. We use k_{ij} as the recruitment rate of single females and males of strains i or j by pairs p_{ij}. Note that $k_{ij} \leq b/4$ for $i \neq j$ and $k_{ii} \leq b/2$, where b is the background per capita birth rate of pairs for a sensitive strain, and that $k_{12} = k_{21}$, because of our assumptions. Then, the pair-formation model for two strains is given by:

$$\begin{aligned}
\dot{m}_1 &= k_{11}p_{11} + k_{12}p_{12} + k_{21}p_{21} - \left(\mu_s + \frac{\sigma}{\theta_1}\right) m_1 - (\varphi_{11}(m, f) + \varphi_{12}(m, f)),\\
\dot{f}_1 &= k_{11}p_{11} + k_{12}p_{12} + k_{21}p_{21} - \left(\mu_s + \frac{\sigma}{\theta_1}\right) f_1 - (\varphi_{11}(m, f) + \varphi_{21}(m, f)),\\
\dot{p}_{11} &= \varphi_{11}(m, f) - \left(\mu_p + \frac{\sigma}{\theta_1}\right) p_{11},\\
\dot{m}_2 &= k_{12}p_{12} + k_{21}p_{21} + k_{22}p_{22} - \left(\mu_s + \frac{\sigma}{\theta_2}\right) m_2 - (\varphi_{21}(m, f) + \varphi_{22}(m, f)),\\
\dot{f}_2 &= k_{12}p_{12} + k_{21}p_{21} + k_{22}p_{22} - \left(\mu_s + \frac{\sigma}{\theta_2}\right) f_2 - (\varphi_{12}(m, f) + \varphi_{22}(m, f)),\\
\dot{p}_{12} &= \varphi_{12}(m, f) - \left(\mu_p + \frac{\sigma}{\theta_1}\right) p_{12},\\
\dot{p}_{21} &= \varphi_{21}(m, f) - \left(\mu_p + \frac{\sigma}{\theta_2}\right) p_{21},\\
\dot{p}_{22} &= \varphi_{22}(m, f) - \left(\mu_p + \frac{\sigma}{\theta_2}\right) p_{22},
\end{aligned} \tag{3.7}$$

where $m = (m_1, m_2)$, $f = (f_1, f_2)$. It is also worth noting that, due to the biology of the parasites — male schistosomes protect and nourish their female partner, while holding them in a copulatory groove — the resistance level of a parasite pair is assumed to be determined by the male member of the pair.

As in Section 2, we will consider the existence and stability of exponential solutions of (3.7) in the case of $\varphi_{ij} = \frac{2\rho_{ij} m_i f_j}{m_1+m_2+f_1+f_2}$. System (3.7) has a three-dimensional subsystem for each schistosome strain. The subsystems are equivalent to system (2.1) with the rates

specified by

$$\begin{aligned}
\dot{m}_i &= k_{ii}\, p_{ii} - \left(\mu_s + \frac{\sigma}{\theta_i}\right) m_i - \varphi(m_i,\, f_i),\\
\dot{f}_i &= k_{ii}\, p_{ii} - \left(\mu_s + \frac{\sigma}{\theta_i}\right) f_i - \varphi(m_i,\, f_i),\\
\dot{p}_{ii} &= \varphi(m_i,\, f_i) - \left(\mu_p + \frac{\sigma}{\theta_i}\right) p_{ii}.
\end{aligned} \tag{3.8}$$

Each of these subsystems admits two trivial exponential solutions

$$(1, 0, 0)\mathrm{e}^{-\left(\mu_s+\frac{\sigma}{\theta_i}\right)t}, \qquad (0, 1, 0)\mathrm{e}^{-\left(\mu_s+\frac{\sigma}{\theta_i}\right)t},$$

which are locally trajectorally unstable with respect to system (3.8) (recall that we have already assumed that $\mu_p < \mu_s$), and a positive exponential solution $(1, 1, \bar{p}_{ii})\mathrm{e}^{\lambda_{p_i} t}$, where

$$\begin{aligned}
\bar{p}_{ii} &= \frac{\rho_{ii}}{\lambda_{p_i} + \mu_p + \frac{\sigma}{\theta_i}},\\
\lambda_{p_i} &= -\frac{1}{2}\left(\mu_s + \mu_p + \rho_{ii} + \frac{2\sigma}{\theta_i}\right) + \frac{1}{2}\sqrt{(\mu_s - \mu_p + \rho_{ii})^2 + 4k_{ii}\rho_{ii}}.
\end{aligned}$$

The unique positive exponential solution is globally trajectorally stable with respect to system (3.8).

We can identify the two equilibria where only one strain persists,

$$E_1 = (1, 1, \bar{p}_{11}, 0, 0, 0, 0, 0), \qquad \text{and} \qquad E_2 = (0, 0, 0, 1, 1, 0, 0, \bar{p}_{22}).$$

Then $E_i \mathrm{e}^{\lambda_{p_i} t}$, which corresponds to the positive exponential solution for a one-strain system, is a persistent solution for each strain, with respect to the whole system (3.7). Next, we consider the stability of these two solutions.

It is not difficult to verify that the Jacobian of system (3.7) at E_1 takes the form

$$J_1 = \begin{pmatrix} A_1 & * & * \\ 0 & A_2 & * \\ 0 & 0 & A_3 \end{pmatrix},$$

where

$$A_1 = \begin{pmatrix} -\mu_s - \dfrac{\sigma}{\theta_1} - \dfrac{1}{2}\rho_{11} & -\dfrac{1}{2}\rho_{11} & k_{11} \\ -\dfrac{1}{2}\rho_{11} & -\mu_s - \dfrac{\sigma}{\theta_1} - \dfrac{1}{2}\rho_{11} & k_{11} \\ \dfrac{1}{2}\rho_{11} & \dfrac{1}{2}\rho_{11} & -\mu_p - \dfrac{\sigma}{\theta_1} \end{pmatrix},$$

$$A_2 = \begin{pmatrix} -\mu_s - \dfrac{\sigma}{\theta_2} - \rho_{21} & 0 & k_{12} & k_{21} \\ 0 & -\mu_s - \dfrac{\sigma}{\theta_2} - \rho_{12} & k_{12} & k_{21} \\ 0 & \rho_{12} & -\mu_p - \dfrac{\sigma}{\theta_1} & 0 \\ \rho_{21} & 0 & 0 & -\mu_p - \dfrac{\sigma}{\theta_2} \end{pmatrix},$$

$$A_3 = -\mu_p - \frac{\sigma}{\theta_2}.$$

The off-diagonal blocks represented by an "$*$" are not of interest for a linear stability analysis. For mathematical convenience, we introduce new symmetric variables, and rearrange the system as:

$$\left(\frac{m_1 + f_1}{2}, p_{11}, \frac{m_1 - f_1}{2}, m_2, f_2, p_{12}, p_{21}, p_{22}\right).$$

With respect to these variables the Jacobian has the form

$$\hat{J}_1 = \begin{pmatrix} A_{11} & * & * & * \\ 0 & A_{12} & * & * \\ 0 & 0 & A_2 & 0 \\ 0 & 0 & 0 & A_3 \end{pmatrix},$$

where

$$A_{11} = \begin{pmatrix} -\mu_s - \dfrac{\sigma}{\theta_1} - \rho_{11} & k_{11} \\ \rho_{11} & -\mu_p - \dfrac{\sigma}{\theta_1} \end{pmatrix}, \qquad A_{12} = -\mu_s - \frac{\sigma}{\theta_1}.$$

The dominant eigenvalue of A_{11} is exactly the exponent λ_{p_1} of the persistent solution when only Strain 1 is present. Note that the off-diagonal entries of A_2 are non-negative. Thus, A_2 has the dominant eigenvalue, denoted by λ_{A_2}, with a strictly positive eigenvector. Therefore, $E_1 e^{\lambda_{p_1} t}$ is trajectorally stable if (i) $\lambda_{p_1} + \mu_s + \frac{\sigma}{\theta_1} > 0$; (ii) $\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2} > 0$; (iii) $\lambda_{p_1} - \lambda_{A_2} > 0$. Condition (i) is equivalent to $\mu_s - \mu_p + k_{11} > 0$, or $\mu_p - \mu_s + \rho_{11} < 0$, which is always satisfied because of $\mu_p < \mu_s$. Condition (ii) is equivalent to

$$\frac{\sigma}{\theta_1} - \frac{\sigma}{\theta_2} < \frac{1}{2}\sqrt{(\mu_s - \mu_p + \rho_{11})^2 + 4k_{11}\rho_{11}} - \frac{1}{2}(\mu_s - \mu_p + \rho_{11}). \tag{3.9}$$

Now, let $\eta = (x, y, p, q)$ be the strictly positive eigenvector associated with the eigenvalue λ_{A_2}. Expanding $(A_2 - \lambda I)\eta = 0$, where I is the identity matrix, we have

$$\left(\mu_s + \rho_{21} + \frac{\sigma}{\theta_2} + \lambda_{A_2}\right) x = k_{12} p + k_{21} q,$$

$$\left(\mu_s + \rho_{12} + \frac{\sigma}{\theta_2} + \lambda_{A_2}\right) y = k_{12} p + k_{21} q,$$

$$\left(\mu_p + \frac{\sigma}{\theta_1} + \lambda_{A_2}\right) p = \rho_{12} y,$$
$$\left(\mu_p + \frac{\sigma}{\theta_2} + \lambda_{A_2}\right) q = \rho_{21} x.$$

Therefore, $\lambda_{A_2} + \mu_p + \frac{\sigma}{\theta_i} > 0$, for $i = 1, 2$, and hence condition (iii) implies condition (ii). Continuing, if we assume that $\rho_{12} = \rho_{21} = \rho$ (i.e., the interstrain pair-formation rate is independent of the strain to which the male belongs), then from the first two equations we have $x = y$. Therefore, it follows that

$$\lambda_{A_2} + \mu_s + \rho + \frac{\sigma}{\theta_2} = \frac{k_{12}\rho}{\lambda_{A_2} + \mu_p + \frac{\sigma}{\theta_1}} + \frac{k_{21}\rho}{\lambda_{A_2} + \mu_p + \frac{\sigma}{\theta_2}}. \tag{3.10}$$

Let

$$f(z) = z + \mu_s + \rho + \frac{\sigma}{\theta_2} - \frac{k_{12}\rho}{z + \mu_p + \frac{\sigma}{\theta_1}} - \frac{k_{21}\rho}{z + \mu_p + \frac{\sigma}{\theta_2}}.$$

Then $f(z)$ is strictly increasing for all positive parameters, and $f(\lambda_{A_2}) = 0$. Note that

$$\lambda_{p_1} + \mu_s + \rho_{11} + \frac{\sigma}{\theta_1} = \frac{k_{11}\rho_{11}}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_1}}. \tag{3.11}$$

If there holds

$$-\rho - \frac{\sigma}{\theta_2} + \frac{k_{12}\rho}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_1}} + \frac{k_{21}\rho}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2}} < -\rho_{11} - \frac{\sigma}{\theta_1} + \frac{k_{11}\rho_{11}}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_1}}, \tag{3.12}$$

then

$$f(\lambda_{p_1}) > \lambda_{p_1} + \mu_s + \rho_{11} + \frac{\sigma}{\theta_1} - \frac{k_{11}\rho_{11}}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_1}} = 0 = f(\lambda_{A_2}),$$

and hence, the monotonicity of $f(z)$ implies that $\lambda_{p_1} > \lambda_{A_2}$ in the case of $\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2} > 0$. Similarly, if the inequality (3.12) is reversed, we have $\lambda_{p_1} < \lambda_{A_2}$. Taken together, we have the following stability conditions for the persistent solution when only Strain 1 is present.

Theorem 3.1. *$E_1 e^{\lambda_{p_1} t}$ is trajectorally stable if $\lambda_{p_1} > \lambda_{A_2}$. In the case of $\rho_{12} = \rho_{21} = \rho$, it is stable if there hold inequalities* (3.9) *and*

$$\frac{\sigma}{\theta_1} - \frac{\sigma}{\theta_2} + \rho_{11} - \rho < \frac{k_{11}\rho_{11} - k_{12}\rho}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_1}} - \frac{k_{21}\rho}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2}}. \tag{3.13}$$

It is unstable in the case of either reversed inequality (3.9) *or $\lambda_{p_1} < \lambda_{A_2}$. In the case of $\rho_{12} = \rho_{21} = \rho$, if inequality* (3.9) *still holds, reversed inequality* (3.13) *can lead to instability of $E_1 e^{\lambda_{p_1} t}$.*

For reasonable parameter values, including those we used in our numerical studies (see Section 4), the condition (3.9) is likely to be satisfied when the condition (3.13) is satisfied.

This allows us to draw the following biological conclusion from Theorem 3.1: Strain 1 can exclude Strain 2 from the population if its growth rate λ_{p_1} exceeds the eigenvalue λ_{A_2}.

In order to study the persistent solution when only Strain 2 exists, $E_2 e^{\lambda_{p_2} t}$, we consider the Jacobian of system (3.7) under the following rearrangement of the variables:

$$\left(m_1,\, p_{12},\, p_{21},\, f_1,\, \frac{m_2+f_2}{2},\, p_{22},\, \frac{m_2-f_2}{2}\right).$$

One can verify that the Jacobian is

$$\hat{J}_2 = \begin{pmatrix} B_1 & * & 0 & 0 \\ 0 & B_2 & 0 & 0 \\ * & * & B_3 & 0 \\ * & * & * & B_4 \end{pmatrix},$$

where

$$B_1 = \begin{pmatrix} -\mu_s - \frac{\sigma}{\theta_1} - \rho_{12} & k_{12} & k_{21} & 0 \\ \rho_{12} & -\mu_p - \frac{\sigma}{\theta_1} & 0 & 0 \\ 0 & 0 & -\mu_p - \frac{\sigma}{\theta_2} & \rho_{21} \\ 0 & k_{12} & k_{21} & -\mu_s - \frac{\sigma}{\theta_1} - \rho_{21} \end{pmatrix},$$

$$B_3 = \begin{pmatrix} -\mu_s - \frac{\sigma}{\theta_2} - \rho_{22} & k_{22} \\ \rho_{22} & -\mu_p - \frac{\sigma}{\theta_2} \end{pmatrix},$$

$$B_2 = -\mu_p - \frac{\sigma}{\theta_1}, \qquad B_4 = -\mu_s - \frac{\sigma}{\theta_2}.$$

Therefore, $E_2 e^{\lambda_{p_2} t}$ is stable if $\lambda_{p_2} + \mu_s + \frac{\sigma}{\theta_2} > 0$, $\lambda_{p_2} + \mu_p + \frac{\sigma}{\theta_1} > 0$, and $\lambda_{p_2} > \lambda_{B_1}$, where λ_{B_1} is the dominant eigenvalue of B_1. Note that the first two inequalities always hold because of $\mu_p < \mu_s$ and $\theta_1 < \theta_2$. In the case where $\rho_{12} = \rho_{21} = \rho$, by the same analysis used for the other equilibrium, we have

$$\lambda_{B_1} + \mu_s + \rho + \frac{\sigma}{\theta_1} = \frac{k_{12}\rho}{\lambda_{B_1} + \mu_p + \frac{\sigma}{\theta_1}} + \frac{k_{21}\rho}{\lambda_{B_1} + \mu_p + \frac{\sigma}{\theta_2}}.$$

Therefore, similar results follow for the persistent solution when Strain 2 excludes Strain 1.

Theorem 3.2. *$E_2 e^{\lambda_{p_2} t}$ is trajectorally stable if $\lambda_{p_2} > \lambda_{B_1}$. In the case where $\rho_{12} = \rho_{21} = \rho$, it is stable if*

$$\frac{\sigma}{\theta_1} - \frac{\sigma}{\theta_2} + \rho - \rho_{22} > \frac{k_{12}\rho}{\lambda_{p_2} + \mu_p + \frac{\sigma}{\theta_1}} + \frac{k_{21}\rho - k_{22}\rho_{22}}{\lambda_{p_2} + \mu_p + \frac{\sigma}{\theta_2}}. \tag{3.14}$$

Again, this persistent solution is stable, and Strain 2 can exclude Strain 1 from the population if the growth rate λ_{p_2} exceeds the eigenvalue λ_{B_1}.

If drug resistance had no cost to parasites, then all parasites would be expected to be made up of only resistant parasites. Since not all parasites are resistant, it is expected that drug-resistant parasites might pay energetic costs that result in lower reproductive rates, or other adverse effects. It would then follow that natural parasite populations in areas where no treatment program exists would maintain very little or no resistance. Thus, it is interesting to consider the situation in which the majority of parasites are resistance free and a small number of individuals that are resistant (either due to a novel mutation or migration from other areas) enter the population. Will the mutant strain, made up of these novel resistant individuals, invade and persist in the population (regardless of whether or not the sensitive strain becomes extinct)?

Let $\theta_1 = 1, \theta_2 > 1$. That is, Strain 1 parasites are fully susceptible and Strain 2 parasites are partially drug resistant. Then, the conditions under which Strain 2 can survive in the population are those under which the persistent solution for Strain 1, $E_1 e^{\lambda_{p_1} t}$, is trajectorally unstable. That is, the instability conditions for $E_1 e^{\lambda_{p_1} t}$ (see Theorem 3.1) provide invasion criteria, and can be used to determine the impact of drug treatment on a mixed population of parasites.

Let us examine the inequalities (3.13) and (3.14) in Theorems 3.1 and 3.2, respectively, in a special case. Assume that the probability of forming a pair between female and male parasites of any two strains is the same, i.e., $\rho_{11} = \rho_{12} = \rho_{21} = \rho_{22} = \rho$. Assume also that there is no reduction in reproduction for the resistant strain, i.e., $k_{11} = k_{22} = b/2$ and $k_{12} = k_{21} = b/4$ where b is the background per capita birth rate of pairs with the sensitive strain. Under these assumptions, the inequalities (3.13) and (3.14) become:

$$\sigma - \frac{\sigma}{\theta_2} < \frac{1/4b\rho}{\lambda_{p_1} + \mu_p + \sigma} - \frac{1/4b\rho}{\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2}}, \tag{3.15}$$

and

$$\sigma - \frac{\sigma}{\theta_2} > \frac{1/4b\rho}{\lambda_{p_2} + \mu_p + \sigma} - \frac{1/4b\rho}{\lambda_{p_2} + \mu_p + \frac{\sigma}{\theta_2}}, \tag{3.16}$$

respectively. Since $\theta_2 > 1$, the inequality (3.15) will never hold as its left hand side is positive and its right hand side is negative. This implies that $E_1 e^{\lambda_{p_1} t}$ is always unstable. $E_2 e^{\lambda_{p_2} t}$ is always stable as its left hand side is positive and its right hand side is negative. Therefore, we have verified the biologically intuitive result:

If there is no cost for drug resistance, then the resistant strain will always invade a population subject to drug treatment, and exclude the sensitive strain.

However, as mentioned above, there is almost certainly some cost that parasites must pay in order to maintain drug resistance, and in Section 4, below, we discuss in more detail one specific form of cost (e.g., reduced reproductive rate) and the effect of such cost. For now, we consider the general case of some reduction in the birth rate for pairs of parasites from the resistant strain. If we take the same assumptions on coefficients as in the above special case, except for $k_{22} = k_{11} h(\theta_2) = b h(\theta_2)/2$, where $h(\theta_2) \in (0, 1)$, then it is easy to see from the inequalities (3.13) and (3.14) that both $E_1 e^{\lambda_{p_1} t}$ and $E_2 e^{\lambda_{p_2} t}$ are unstable for all sufficiently small $h(\theta_2)$. In this case, coexistence of the two strains is expected, due

to the cost paid by the resistant Strain 2. Next, we consider the possibility of coexistence of the two strains in the general setting.

Consider the functions $m_i = \bar{m}_i e^{\lambda t}$, $f_i = \bar{f}_i e^{\lambda t}$, $p_{ij} = \bar{p}_{ij} e^{\lambda t}$, where $\bar{m}_i$, $\bar{f}_i$, $\bar{p}_{ij} > 0$, $i, j = 1, 2$. These functions are the components of the exponential solution of system (3.7) if and only if

$$
\begin{aligned}
&k_{11}\bar{p}_{11} + k_{12}\bar{p}_{12} + k_{21}\bar{p}_{21} - \left(\lambda + \mu_s + \frac{\sigma}{\theta_1}\right)\bar{m}_1 \\
&\quad - (\varphi_{11}(\bar{m}, \bar{f}) + \varphi_{12}(\bar{m}, \bar{f})) = 0, \\
&k_{11}\bar{p}_{11} + k_{12}\bar{p}_{12} + k_{21}\bar{p}_{21} - \left(\lambda + \mu_s + \frac{\sigma}{\theta_1}\right)\bar{f}_1 \\
&\quad - (\varphi_{11}(\bar{m}, \bar{f}) + \varphi_{21}(\bar{m}, \bar{f})) = 0, \\
&k_{12}\bar{p}_{12} + k_{21}\bar{p}_{21} + k_{22}\bar{p}_{22} - \left(\lambda + \mu_s + \frac{\sigma}{\theta_2}\right)\bar{m}_2 \\
&\quad - (\varphi_{21}(\bar{m}, \bar{f}) + \varphi_{22}(\bar{m}, \bar{f})) = 0, \\
&k_{12}\bar{p}_{12} + k_{21}\bar{p}_{21} + k_{22}\bar{p}_{22} - \left(\lambda + \mu_s + \frac{\sigma}{\theta_2}\right)\bar{f}_2 \\
&\quad - (\varphi_{12}(\bar{m}, \bar{f}) + \varphi_{22}(\bar{m}, \bar{f})) = 0, \\
&\varphi_{11}(\bar{m}, \bar{f}) - \left(\lambda + \mu_p + \frac{\sigma}{\theta_1}\right)\bar{p}_{11} = 0, \\
&\varphi_{12}(\bar{m}, \bar{f}) - \left(\lambda + \mu_p + \frac{\sigma}{\theta_1}\right)\bar{p}_{12} = 0, \\
&\varphi_{21}(\bar{m}, \bar{f}) - \left(\lambda + \mu_p + \frac{\sigma}{\theta_2}\right)\bar{p}_{21} = 0, \\
&\varphi_{22}(\bar{m}, \bar{f}) - \left(\lambda + \mu_p + \frac{\sigma}{\theta_2}\right)\bar{p}_{22} = 0,
\end{aligned}
\tag{3.17}
$$

where $\bar{m} = (\bar{m}_1, \bar{m}_2)$, and $\bar{f} = (\bar{f}_1, \bar{f}_2)$.

Again taking $\rho_{12} = \rho_{21} = \rho$, we try to find strictly positive solutions of system (3.17) with $\bar{m}_i = \bar{f}_i$. Substituting the last four equations into the first four equations in (3.17), we have

$$
\begin{aligned}
\lambda + \mu_s + \frac{\sigma}{\theta_1} + \frac{\rho_{11}\bar{m}_1 + \rho\bar{m}_2}{\bar{m}_1 + \bar{m}_2} &= \frac{k_{11}\rho_{11}\bar{m}_1 + k_{12}\rho\bar{m}_2}{(\lambda + \mu_p + \frac{\sigma}{\theta_1})(\bar{m}_1 + \bar{m}_2)} \\
&\quad + \frac{k_{21}\rho\bar{m}_2}{(\lambda + \mu_p + \frac{\sigma}{\theta_2})(\bar{m}_1 + \bar{m}_2)}, \\
\lambda + \mu_s + \frac{\sigma}{\theta_2} + \frac{\rho_{22}\bar{m}_2 + \rho\bar{m}_1}{\bar{m}_1 + \bar{m}_2} &= \frac{k_{21}\rho\bar{m}_1 + k_{22}\rho_{22}\bar{m}_2}{(\lambda + \mu_p + \frac{\sigma}{\theta_2})(\bar{m}_1 + \bar{m}_2)} \\
&\quad + \frac{k_{12}\rho\bar{m}_1}{(\lambda + \mu_p + \frac{\sigma}{\theta_1})(\bar{m}_1 + \bar{m}_2)}.
\end{aligned}
$$

As in Castillo-Chavez et al. (1996), if we define $T = \frac{\bar{m}_2}{\bar{m}_1+\bar{m}_2}$, then it follows that

$$\begin{aligned}
&\lambda + \mu_s + \frac{\sigma}{\theta_1} + \rho_{11}(1-T) + \rho T - \frac{k_{11}\rho_{11}(1-T) + k_{12}\rho T}{\lambda + \mu_p + \frac{\sigma}{\theta_1}} \\
&\quad - \frac{k_{21}\rho T}{\lambda + \mu_p + \frac{\sigma}{\theta_2}} = 0, \\
&\lambda + \mu_s + \frac{\sigma}{\theta_2} + \rho_{22} T + \rho(1-T) - \frac{k_{21}\rho(1-T) + k_{22}\rho_{22} T}{\lambda + \mu_p + \frac{\sigma}{\theta_2}} \\
&\quad - \frac{k_{12}\rho(1-T)}{\lambda + \mu_p + \frac{\sigma}{\theta_1}} = 0.
\end{aligned} \tag{3.18}$$

Lemma 3.1. *In the case of $\rho_{12} = \rho_{21} = \rho$, system (3.17) admits a strictly positive solution with $\bar{m}_i = \bar{f}_i$, $i = 1, 2$, if and only if there exist a real number λ and a number $T \in (0, 1)$ satisfying Eqs. (3.18).*

If the boundary exponential solutions $E_i e^{\lambda_{p_i} t}$, for $i = 1, 2$, lose their stability due to the inequalities (3.13) and (3.14), then we have the existence of strictly positive persistent solutions which allow the two strains to coexist.

Theorem 3.3. *In the case where $\rho_{12} = \rho_{21} = \rho$, if $E_i e^{\lambda_{p_i} t}$, for $i = 1, 2$, are unstable because of the reversed inequalities (3.13) and (3.14), then system (3.7) admits at least one persistent solution for two strains coexisting.*

Proof. Denote the left hand sides of equations in (3.18) by $G_1(\lambda, T)$ and $G_2(\lambda, T)$, respectively. Let $\alpha = -\mu_p - \min\{\frac{\sigma}{\theta_1}, \frac{\sigma}{\theta_2}\}$. A direct computation shows that $\frac{\partial G_i}{\partial \lambda}(\lambda, T) > 0$ for all $T \in [0, 1]$ and $\lambda \in (\alpha, +\infty)$, and that for each $T \in (0, 1)$, $\lim_{\lambda \to \alpha^+} G_i(\lambda, T) = -\infty$, $\lim_{\lambda \to +\infty} G_i(\lambda, T) = \infty$. Therefore, for each $T \in (0, 1)$, there exists a unique $\lambda_i(T)$ such that $G_i(\lambda_i(T), T) = 0$. Furthermore, by the implicit function theorem, $\lambda_i(T)$ are continuous functions of T on $(0, 1)$. Note that the equalities (3.10) and (3.11) show that $G_2(\lambda_{A_2}, 0) = 0$ and $G_1(\lambda_{p_1}, 0) = 0$. Thus, together with the reversed inequalities (3.13) and (3.14), the implicit function theorem implies that

$$\lambda_2(0) = \lambda_{A_2} > \lambda_{p_1} = \lambda_1(0).$$

The same argument leads to $\lambda_1(1) = \lambda_{B_1} > \lambda_2(1) = \lambda_{p_2}$. By the continuity of $\lambda_i(T)$ on T, there exists at least one $T^* \in (0, 1)$ such that $\lambda_1(T^*) = \lambda_2(T^*)$. Hence, Lemma 3.1 completes the proof.

4. Impact of treatment on coexistence of strains

In this section, we discuss further the impact of drug treatment on drug-resistant schistosomes, and conduct some numerical simulations to verify and extend our analytic results. To incorporate the costs that parasites are paying for the drug resistance, we assume that the birth rates of pairs that involve Strain 2 parasites are decreasing functions of θ_2. Thus, parasite reproductive capacity and drug resistance are inversely related. Let $k_{12} = k_{21} = k_{11}/(2\theta_2)$, $k_{22} = k_{11}/(3\theta_2)$. With regard to the mating possibilities between

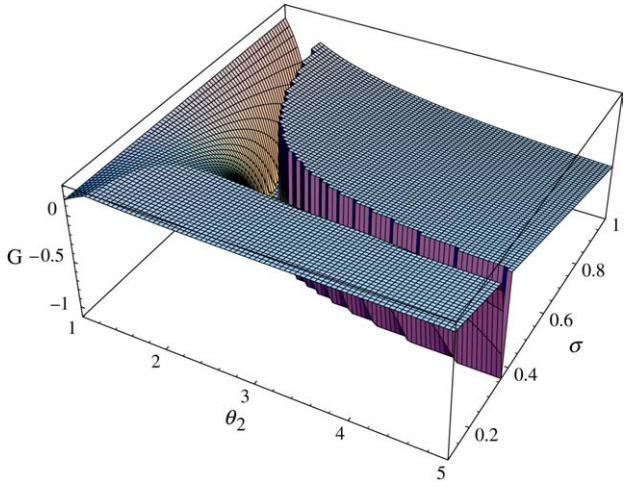

Fig. 1. The plot of function $G(\sigma, \theta_2)$. The invasion condition for Strain 2 parasites is $G(\sigma, \theta_2) < 0$.

the strains, we assume that $\rho_{11} = \rho_{22} = 3\rho/2$, and $\rho_{12} = \rho_{21} = \rho$, which taken together imply that individuals of the same strain are more likely to encounter one another and form a mated pair than individuals of different strains. We also retain the assumption that $\mu_s = 10\mu_p$, reflecting the diminished survival experienced by unmated worms.

We then, rewrite (3.13) and (3.14) as $F_1(\sigma, \theta_2) > 0$ and $F_2(\sigma, \theta_2) > 0$, respectively, where

$$F_1(\sigma, \theta_2) = \frac{\sigma}{\theta_2} - \sigma - \frac{1}{2}\rho + \frac{(1 - \frac{1}{2\theta_2})k_{11}\rho}{\lambda_{p_1} + \mu_p + \sigma} - \frac{k_{11}\rho}{2\theta_2(\lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2})},$$

$$F_2(\sigma, \theta_2) = \sigma - \frac{\sigma}{\theta_2} - \frac{1}{2}\rho - \frac{(\frac{1}{2\theta_2} - \frac{1}{3\theta_2})k_{11}\rho}{\lambda_{p_2} + \mu_p + \frac{\sigma}{\theta_2}} - \frac{k_{11}\rho}{2\theta_2(\lambda_{p_2} + \mu_p + \sigma)}.$$

Let $f(\sigma, \theta_2) = \lambda_{p_1} + \mu_p + \frac{\sigma}{\theta_2}$, $G(\sigma, \theta_2) = \min\{F_1(\sigma, \theta_2), f(\sigma, \theta_2)\}$. Then the invasion condition for Strain 2 parasites is $G(\sigma, \theta_2) < 0$ (Fig. 1). According to Theorem 3.3, in the case of $f(\sigma, \theta_2) > 0$, the coexistence domain is

$$\Omega = \{(\sigma, \theta_2) : F_i(\sigma, \theta_2) < 0, i = 1, 2\},$$

which is shown in Fig. 2. L_i represents the curve on which $F_i(\sigma, \theta_2) = 0$, while l represents the curve $f(\sigma, \theta_2) = 0$. Below the curve L_1 is the domain where the Strain 1 persistent solution $E_1 e^{\lambda_{p_1} t}$ is stable, and the resistant Strain 2 can not invade the population. Above the curve L_2, $E_2^{\lambda_{p_2} t}$ is stable, and the resistant Strain 2 will take over the population, excluding the susceptible Strain 1. The parameter values used for the figures are taken as $k_{11} = 0.5$, $\mu_s = 0.2$, $\rho = 0.467$.

We numerically calculated the solutions of the proportion system corresponding to (3.7). In Fig. 3, all parameters have the same values as in Figs. 1 and 2, and the resistance level of Strain 2 is set at $\theta_2 = 2.5$. For this level of resistance, $F_1(\sigma, 2.5) = 0$ at $\sigma = 0.359$, and $F_2(\sigma, 2.5) = 0$ at $\sigma = 0.583$. Thus, in Fig. 2, $(\sigma, \theta_2) = (0.32, 2.5)$ represents a point

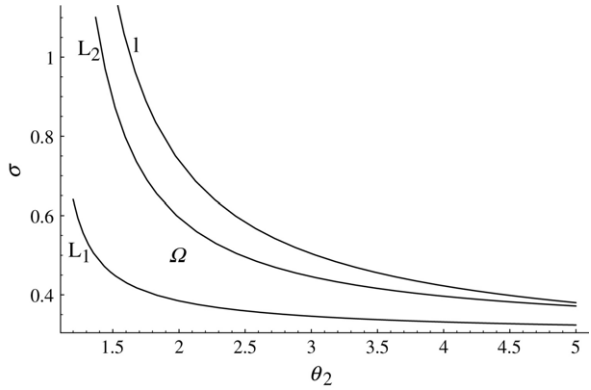

Fig. 2. The plots of curves $F_i(\sigma, \theta_2) = 0$ and $f(\sigma, \theta_2) = 0$. Below the curve L_1 is the parameter domain where the Strain 1 persistent solution is stable, while the Strain 2 persistent solution is stable above the curve L_2. Ω is the coexistence domain.

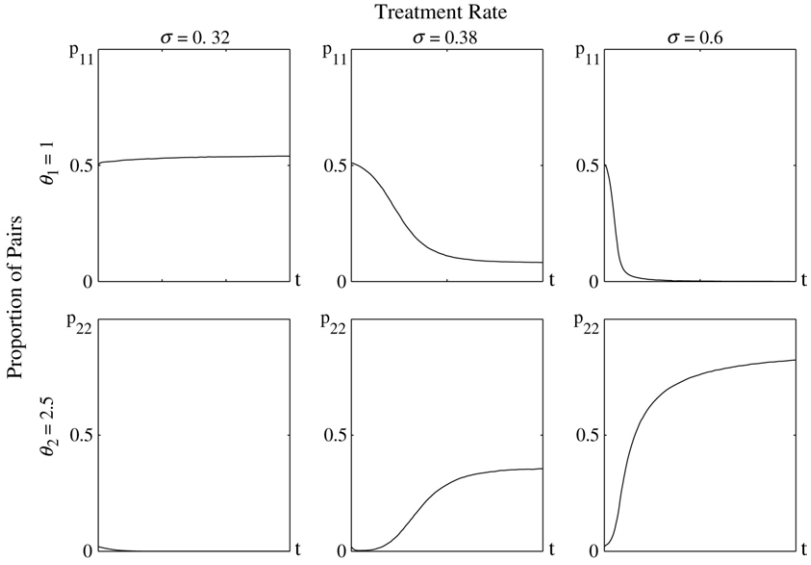

Fig. 3. The proportions of pairs p_{11} and p_{22} in the whole population vs. time t, plotted for three different treatment rates. The parameter values are the same as for Figs. 1 and 2. For this set of values, $F_1(\sigma, 2.5) = 0$ when $\sigma = 0.36$ and $F_2(\sigma, 2.5) = 0$ when $\sigma = 0.583$.

slightly below the curve L_1, and hence, the Strain 1 persistent solution is stable (Fig. 3, left column). The point $(\sigma, \theta_2) = (0.38, 2.5)$ lies slightly above the curve L_1 and belongs to the domain Ω, and so the Strain 1 persistent solution is unstable, and there exists a persistent solution for coexistence of the two strains; in this case, the coexistence is stable (Fig. 3, middle column). For the point $(\sigma, \theta_2) = (0.6, 2.5)$, which is slightly above the curve L_2, the Strain 2 persistent solution is stable (Fig. 3, right column).

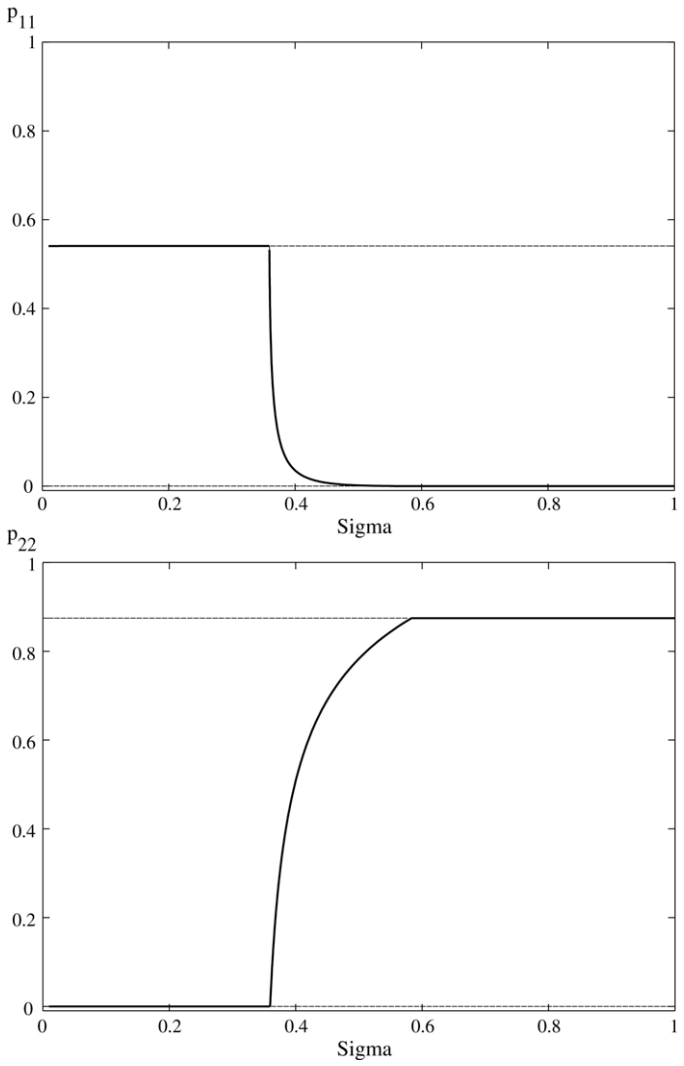

Fig. 4. The bifurcation diagrams, regarding σ as the bifurcation parameter, for the proportions of pairs p_{11} and p_{22}, where all parameters are the same except for $\theta_2 = 2.5$.

In order to visualize the bifurcation described in Fig. 2 more clearly, we used Auto to plot the proportions of the pairs p_{11} and p_{22} in the whole population (Fig. 4), again using σ as the bifurcation parameter and taking $\theta_2 = 2.5$. The solid lines imply that the corresponding persistent solution is trajectorally stable while the dashed lines represent the instability of the corresponding persistent solution. For $\sigma < 0.359$, the Strain 1 persistent solution is stable; for $\sigma \in (0.36, 0.583)$, the persistent solution for coexistence is stable; and for $\sigma > 0.584$, the Strain 2 persistent solution becomes stable. Therefore, as long as $\sigma > 0.36$, Strain 2 will invade and persist in the population.

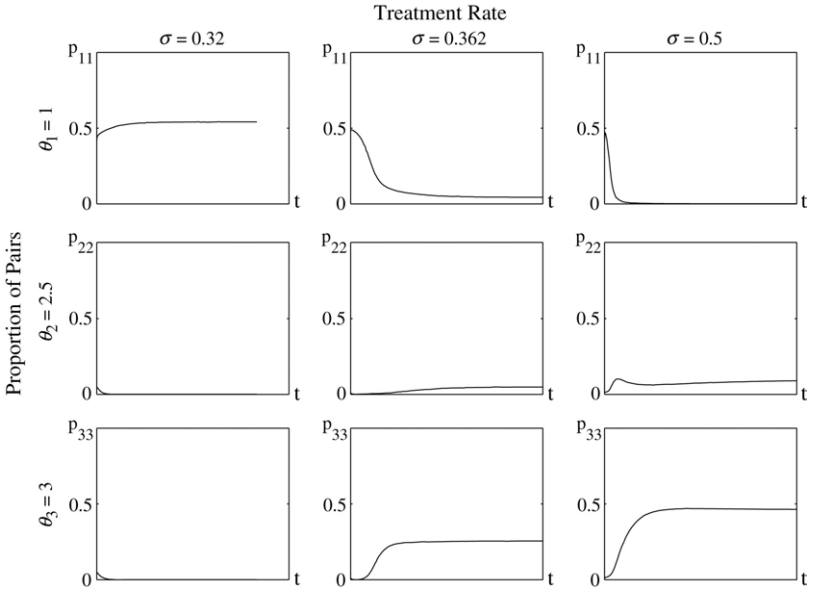

Fig. 5. Simulations of proportions of pairs for various values of the treatment rate σ and three parasite strains: $\theta_1 = 1$ (susceptible strain), $\theta_2 = 2.5$ and $\theta_3 = 3$.

From these computations, we have the following observations:

(1) Higher treatment rates can allow parasites with lower drug resistance to invade (see Fig. 2).

(2) Higher treatment rate can allow for coexistence between susceptible and resistant parasite strains, though the range of "allowable" resistance levels becomes more narrow, and can result in the elimination of both susceptible and highly resistant parasite strains from the population (Fig. 2).

(3) There exists a critical value σ_c such that for $\sigma < \sigma_c$, the drug-resistant strain can not invade and persist in the population (see Figs. 2 through 4), where $\sigma_c = -\frac{1}{2}\rho_{11} + \frac{k_{11}\rho_{11}}{\alpha} > 0$, where $\alpha = -\frac{1}{2}(\mu_s - \mu_p + \rho_{11}) + \frac{1}{2}\sqrt{(\mu_s - \mu_p + \rho_{11})^2 + 4k_{11}\rho_{11}}$.

Briefly, we can also consider the behavior of the model for multiple strains (>2). For three strains — one susceptible strain ($\theta_1 = 1$) and two drug-resistant strains ($\theta_3 > \theta_2 > 1$) — the simulations of the proportions of "same strain" pairs in the whole population are shown in Fig. 5. Costs are of the form used in the two-strain model above except for $k_{13} = k_{31} = k_{11}/(2\theta_3)$, $k_{23} = k_{32} = k_{11}/(3.5\theta_3)$, $k_{33} = k_{11}/(4\theta_3)$. Parameter values are as above, except for drug resistance levels: $\theta_2 = 2.5$ and $\theta_3 = 3$. Simulation results show that for a treatment rate $\sigma < 0.345$, only the sensitive Strain 1 persists; and for $\sigma > 0.346$, drug resistant strains can begin to invade the population. In Fig. 5, the three strains coexist in the case of $\sigma = 0.362$ (middle column), and the sensitive strain becomes extinct and only the drug resistant strains coexist for $\sigma > 0.39$ (right column).

5. Discussion

The control of schistosomiasis continues to be difficult due, at least in part, to the complexity of the parasites themselves. The use of multiple hosts, the presence of separate sexes, widespread genetic diversity, and other factors all contribute to this complexity; together, they are likely to have a significant impact on attempts to control the disease through chemotherapeutic treatment of human patients. These factors also complicate attempts to realistically model the transmission of schistosome parasites. The approach that we have used to date has focused on analyzing how these factors in isolation affect the interplay between drug treatment and parasite genetic diversity (i.e., the number of different parasite strains in the population). Such analyses provide estimates for the various model parameters that are needed to yield biologically intuitive results, as well as drive hypothesis testing in laboratory and field-based studies of these parasites. For example, the results presented above suggest that it will be important to determine the extent of protection that a male schistosome can impart to his mate based on his genetically determined drug resistance.

In the current model, such protection allows a drug resistant male to shelter a more susceptible (but also more fertile) female, thereby leaving more offspring that carry his genes in the next generation. The male worm benefits by mating with a more fecund female from the susceptible strain, and the female worm benefits by out-living (and out-producing) her peers that were mated to, and not protected by, males from the susceptible strain. While this feature of the model is based on our understanding of how drugs like Praziquantel kill schistosomes, further experimentation is needed to determine if protection occurs to the extent described in our model, if at all.

Other areas of biological research are also highlighted by our current model as being important for further refinement of the model, and to improve our understanding of schistosome population dynamics and the control of schistosomiasis. Further studies of inter-strain matings are needed that investigate factors such as mate choice by male and female worms, and the sex ratio of the offspring produced. The need for further genetic studies of natural schistosome populations is also indicated. Such studies will provide critical insight into the range of genetic polymorphism present in these populations on different geographic scales, and the likely impact of gene flow and selection imposed by control efforts on the spread of drug resistance.

In summary, the current model describes how the interaction between schistosome strains with a range of susceptibility to drug treatments can lead to a stable genetic polymorphism in the population. It also predicts parameters and features that would be required to allow drug resistant worms to invade, become established within, and perhaps even replace a formerly susceptible population of worms. The results of the deterministic model for two strains have also been extended through numerical studies and shown to be qualitatively similar for three strains. Further refinement of the model might attempt to incorporate further elements of complexity in the schistosomiasis system, such as the interactions among the larval stages of various strains within the snail intermediate hosts.

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