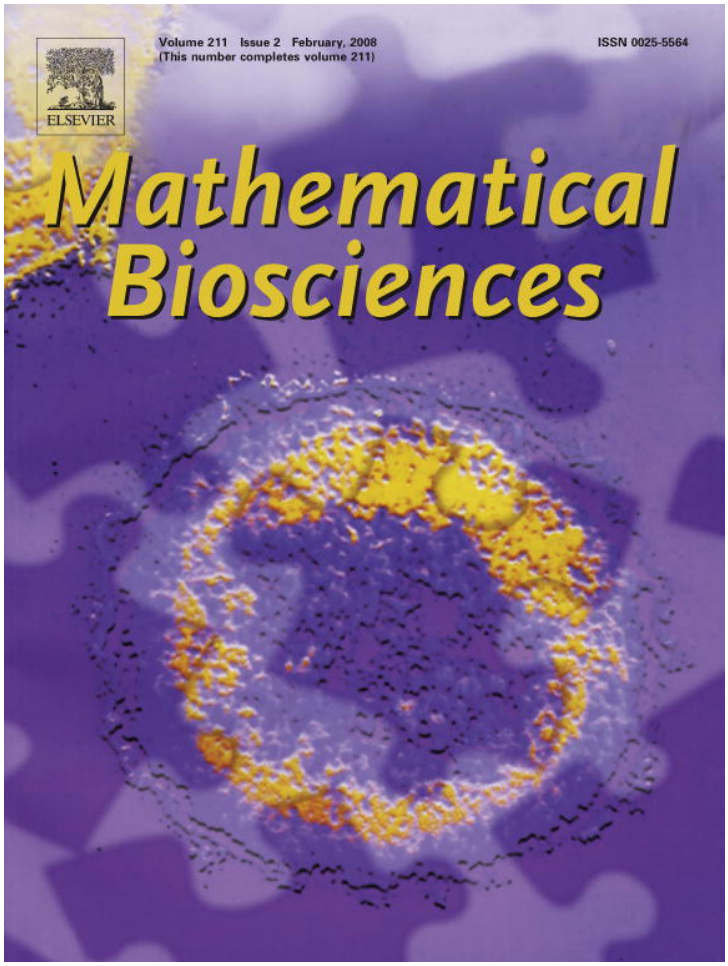

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A schistosomiasis model with mating structure and time delay

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Abstract

A system of homogeneous equations with a time delay is used to model the population dynamics of schistosomes. The model includes the parasite's mating structure, multiple resistant schistosome strains, and biological complexity associated with the parasite's life cycle. Invasion criteria of resistant strains and coexistence threshold conditions are derived. These results are used to explore the impact of drug treatment on resistant strain survival. Numerical simulations indicate that the dynamical behaviors of the current model are not qualitatively different from those derived from an earlier model that ignores the impact of time delays associated with the multiple stages in parasite's life cycle. However, quantitatively the time delays make it more likely for drug-resistant strains to invade in a parasite population.

Keywords: Homogeneous equations; Time delay; Schistosome mating structure; Multiple strains; Drug resistance

1. Introduction

The expansion of agricultural and water resources that come hand in hand with population and economic growth in developing nations have facilitated the growth and evolution of schistosomiasis. Recent estimates suggest that there are 200 million individuals are infected worldwide and 600 million at risk worldwide [4]. Children are especially vulnerable to infection, which develops into chronic disease if not treated [17]. Current control programs primarily focus on chemotherapy with praziquantel (PZQ), a chemical that reduces morbidity by killing adult worms and halting the deposition of parasite eggs within treated human hosts. Not surprisingly, systematic efforts to control schistosomiasis in human populations through drug treatment establishes an additional selective force that impacts genetic variation within the parasite population. Current evidence supports the view that natural schistosome strains exhibit varying resistance to treatment with PZQ [5,7,14]. Nevertheless, the subject of schistosome resistance to chemotherapy has just begun to receive attention. In fact, most mathematical models of schistosomiasis do not consider drug resistance of the parasites. In this article we expand our initial efforts to address the role of treatment on the genetic variation of schistosomiasis.

The impact of alternative host treatment rates can affect, as it was shown in earlier work, the range of strains that may be selected by the schistosome population [8,18]. In these modeling efforts, it was assumed that strains with higher resistance levels pay higher costs which reduce transmission. It was also shown that increasing treatment rates favors not only strains with higher levels of resistance (despite the costs) but also strain variability. The model in [8] considered definitive (human) and intermediate (snail) hosts while allowing for an aggregated distribution of parasites in the definitive host population. In order to keep the model manageable, schistosome mating behaviors were ignored in [8]. Previous studies have suggested that mating structure may play an important role in the study of pop-

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ulation dynamics [2,3,6,10,12,15]. Since the resistance level of a parasite pair is determined by the male's (because male schistosomes protect and nourish their female partners while holding them in a copulatory groove), models that incorporate mating need also to be explored [18]. The introduction of the schistosome's mating structure in a multi-strain system greatly increases model complexity even without considering explicit host population dynamics. As a starting point, the model in [18] ignored several stages of the parasite's complex life cycle (see Fig. 1). It considers only the adult parasite populations while assuming that the recruitment rate of single adult parasites at time t depends instantaneously on the total number of parasite pairs at time t.

In this paper, we relax this assumption on the parasite's life history by introducing a time delay that accounts for the average time that must elapse between two adult generations. The life cycle of schistosomes includes several stages as shown in Fig. 1: schistosomulum (larval stage), adult schistosome, egg, free-swimming miracidium, sporocyst and cercaria. It is about 5 weeks from the time of cercaria penetration through skins of human hosts to the time when embrionated eggs are discharged, and cercariae are produced about 4 weeks after the miracidium penetration in snail hosts. The free-living stages are short (1–2 days) but miracidia and cercariae have very high death rates due to the small probability of getting in contact and successful penetration of a host. In this paper we incorporate these processes by considering the probability of survival in each stage and the times required to complete these stages. The goal of this study is to determine whether addition of details on the parasite's life-history influences the impact of drug treatment on the dynamics of multiple stains of schistosomes.

The model in this paper maintains the mating system, the parasite's drug resistance assumption and the reproductive costs from resistance [18]. Here, first we consider a one-strain model with a time delay, and existence and stability results are obtained. These results are used to analyze a two-strain model. Numerical simulations that confirm the analytic results and examine the impact of the time delay are conducted. The overall results in this paper are similar to those given in previous research. That is, drug treatments affect the variety of strains that can coexist in the parasite population. It may even lead to the exclusion of susceptible strains. Numerical observations suggest that the parameter region for invasion and persistence of resistant strains increase as the magnitude of the time delay increases and the time delay makes it more likely for resistant strains to invade and persist in a parasite population.

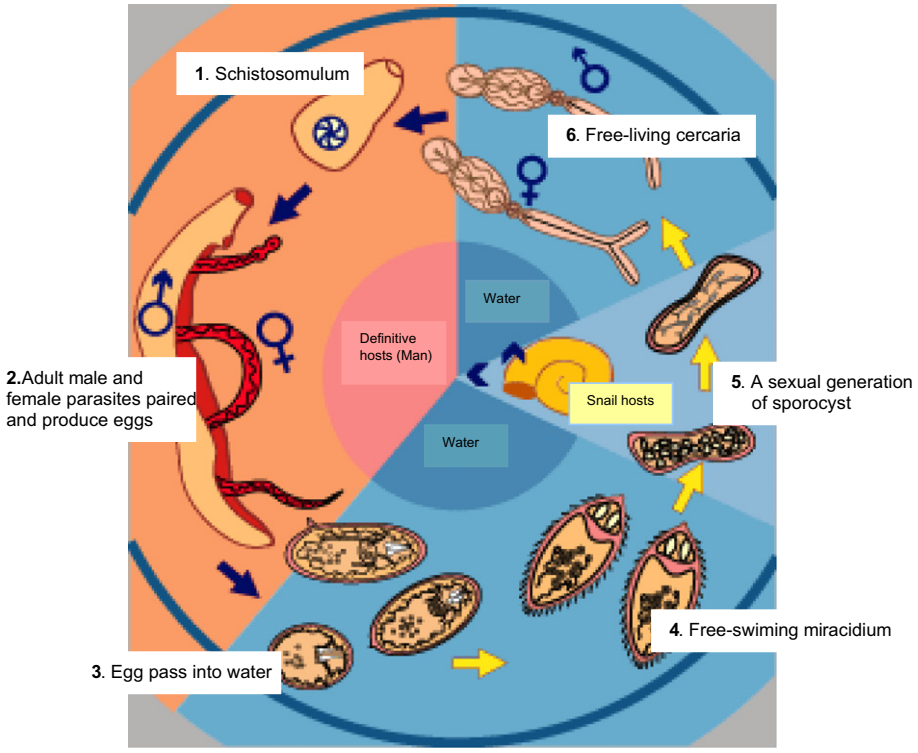

Fig. 1. The life cycle of *Schistosoma mansoni*. (1) Schistosomula (larval stage) are formed after cercariae penetrate the skins of definitive human hosts. (2) After about 5 weeks paired adult male and female parasites start producing eggs some of which become mature and pass into the environment (water). (3) Miracidia hatch from the egg in water and penetrate the intermediate snail hosts. (4) Sporocyst is developed from the miracidium after the penetration. (5) After about 4 weeks, sporocyst begins its asexual multiplication and thousands of cercariae are released into water. (6) In water cercariae infect the definitive hosts by penetrating the skins of human hosts, and after the penetration the larval stage of schistosome begins. This figure is a modification of figures published by WHO [17].

2. The models and their analysis

The models presented here generalize those considered in [18]. The two-strain non-delay model is given by the following system:

$$\begin{aligned}
\dot{m}_i &= B_i(t) - \left(\mu_m + \frac{\sigma}{\theta_i}\right)m_i - \sum_{j=1}^{2}\varphi_{ij}(m,f),\\
\dot{f}_i &= B_i(t) - \left(\mu_f + \frac{\sigma}{\theta_i}\right)f_i - \sum_{j=1}^{2}\varphi_{ji}(m,f),\\
\dot{p}_{ij} &= \varphi_{ij}(m,f) - \left(\mu_p + \frac{\sigma}{\theta_i}\right)p_{ij},\\
B_i(t) &= k_{ii}p_{ii}(t) + k_{12}p_{12}(t) + k_{21}p_{21}(t), \quad i,j = 1,2.
\end{aligned} \tag{2.1}$$

From this system we see that the adult schistosome population is divided into eight subgroups where

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, i, j=1, 2.

$m = (m_1, m_2), f = (f_1, f_2), B_i$ denotes the recruitment rate of type i single parasites and k_{ij} is related to the reproduction rate by pairs p_{ij}. It is assumed that $k_{ij} \leqslant b/4$ for $i \neq j$ and $k_{ii} \leqslant b/2$, where b represents a background per capita birth rate of pairs with sensitive strains; μ_m, μ_f and μ_p denote the per capita death rates of single male, female worms and worms in a mated pair, respectively. In reality, mated pairs can live for a few years while single parasites may live only for a few months [1]. Thus, we assume $\mu_m, \mu_f > \mu_p$. The drug-sensitive parasite strain has an additional per capita death rate, σ, due to treatment. For a parasite strain that has developed drug resistance with a resistance level $\theta(\theta > 1)$, this treatment-related death rate is assumed to be reduced by the factor θ to σ/θ. As in [18], the resistance level of a parasite pair is again assumed to be determined by that of the male parasite due to the biology of the parasites. φ_{ij} describes the rate of pair formation and it is taken to be of the form $\varphi_{ij} = \frac{2\rho_{ij}m_i f_j}{m_1+m_2+f_1+f_2}$, where $2\rho_{ij}$ 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 [15]).

In Model (2.1), the recruitment rates of single adult parasites at time t are assumed to depend on the total number of parasite pairs at the same time t. That is, the model ignores the time parasites spent during the non-adult part of their life cycle which can be as long as a couple of months. Below, we modify the system and incorporate life-history effects by introducing a fixed time delay, τ, in the recruitment terms. The analysis of the one-strain system with a time delay follows.

2.1. Analysis of a one-strain system with delay

If only one-strain is present in the population, the model with a time delay reads

$$\begin{aligned}
\dot{m}(t) &= kS_m(\tau)p(t-\tau) - \left(\mu_m + \frac{\sigma}{\theta}\right)m(t) - \varphi(m(t),f(t)),\\
\dot{f}(t) &= kS_f(\tau)p(t-\tau) - \left(\mu_f + \frac{\sigma}{\theta}\right)f(t) - \varphi(m(t),f(t)),\\
\dot{p}(t) &= \varphi(m(t),f(t)) - \left(\mu_p + \frac{\sigma}{\theta}\right)p(t).
\end{aligned} \tag{2.2}$$

Here, $S_m(\tau)$ and $S_f(\tau)$ are functions which keep track of both the parasite's survival probabilities in various (non-adult) stages of the life cycle. $S_m(\tau)$ and $S_f(\tau)$ may take the form of a product of factors representing the probability of an egg getting into snail contaminated water; the probability of successfully infecting a snail; the number of cercaria generated by one miracidium within the snail (this number depends on the snail's infection age and there is a latent period during which no cercariae are produced); and the probability that a cercaria successfully infect a human host and survive the larval stage to become an adult schistosome. The time delay, τ, is assumed to capture various effects. For example, once an egg gets into water, a miracidium hatches from the egg and it can survive for only 1–2 days if it cannot find and successfully infect a snail. Similarly, a cercaria can survive for only 1–2 days if it cannot find and infect a human host. An infected snail is assumed to have an average life span of 170 days which includes a latent period of a few weeks. Specific forms for $S_m(\tau)$ and $S_f(\tau)$ are given in Section 3. All variables and parameters in (2.2) have the same meaning as in Model (2.1) except that the subscripts are dropped/changed and the fixed time delay (τ) is introduced in the recruitment terms.

System (2.2) is a homogeneous system [10–13], hence, we look for persistent distribution, i.e., exponential solutions of the form

$$(m(t),f(t),p(t)) = (\bar{m},\bar{f},\bar{p})e^{\bar{\lambda}t} = (\bar{m}(\tau),\bar{f}(\tau),\bar{p}(\tau))e^{\bar{\lambda}(\tau)t}.$$

Direct substitution in (2.2) gives the nonlinear system

$$\begin{aligned}
kS_m(\tau)e^{-\lambda\tau}\bar{p} - \left(\mu_m + \frac{\sigma}{\theta}\right)\bar{m} - \varphi(\bar{m},\bar{f}) &= \lambda\bar{m},\\
kS_f(\tau)e^{-\lambda\tau}\bar{p} - \left(\mu_f + \frac{\sigma}{\theta}\right)\bar{f} - \varphi(\bar{m},\bar{f}) &= \lambda\bar{f},\\
\varphi(\bar{m},\bar{f}) - \left(\mu_p + \frac{\sigma}{\theta}\right)\bar{p} &= \lambda\bar{p},
\end{aligned} \tag{2.3}$$

which supports two trivial solutions (up to a constant)

$$E_m = (1,0,0) \text{ and } E_f = (0,1,0) \text{ with } \lambda_m = -\mu_m - \frac{\sigma}{\theta} \text{ and } \lambda_f = -\mu_f - \frac{\sigma}{\theta}. \tag{2.4}$$

In addition, from Eq. (2.3) it follows that

$$\lambda(\bar{p}+\bar{m}) = \left(kS_m(\tau)e^{\lambda\tau} - \mu_p - \frac{\sigma}{\theta}\right)\bar{p} - \left(\mu_m + \frac{\sigma}{\theta}\right)\bar{m},$$

or, if $\bar{p} \neq 0$, that

$$\frac{\bar{m}}{\bar{p}} = \frac{kS_m(\tau)e^{-\lambda\tau} - \mu_p - \frac{\sigma}{\theta} - \lambda}{\lambda + \mu_m + \frac{\sigma}{\theta}}.$$

Similarly, we have that

$$\frac{\bar{f}}{\bar{p}} = \frac{kS_f(\tau)e^{-\lambda\tau} - \mu_p - \frac{\sigma}{\theta} - \lambda}{\lambda + \mu_f + \frac{\sigma}{\theta}}.$$

From the third equation in (2.3),

$$\varphi\left(\frac{\bar{m}}{\bar{p}}, \frac{\bar{f}}{\bar{p}}\right) = \lambda + \mu_p + \frac{\sigma}{\theta}. \tag{2.5}$$

Hence, positive solutions exist only if $\lambda + \mu_p + \frac{\sigma}{\theta} > 0$ and if $\frac{\bar{m}}{\bar{p}}, \frac{\bar{f}}{\bar{p}} > 0$, that is, if

$$\begin{aligned} &kS_m(\tau)e^{-\lambda\tau} - \mu_p - \frac{\sigma}{\theta} - \lambda > 0, \quad \text{and} \\ &kS_f(\tau)e^{-\lambda\tau} - \mu_p - \frac{\sigma}{\theta} - \lambda > 0. \end{aligned} \tag{2.6}$$

Consequently, as λ increases from $-\mu_p - \sigma/\theta$ to the upper bound determined by (2.6), the left side of (2.5) decreases monotonically from a positive value to zero, whereas the right side increases monotonically from zero to a positive value. Therefore, (2.5) admits a unique solution $\bar{\lambda} > -\mu_p - \sigma/\theta$. That is, there exists a unique positive exponential solution $(\bar{m}, \bar{f}, \bar{p})e^{\bar{\lambda}t}$. In the case when $S_m(\tau) = S_f(\tau)$ and $\mu_m = \mu_f$, the positive solution is given by $(1, 1, \bar{p})e^{\bar{\lambda}t}$ where $\bar{p} = \rho/(\bar{\lambda} + \mu_p + \sigma/\theta)$.

Hadeler's results [11] imply that the stability of the positive exponential solution can be determined by the location of the eigenvalues of the eigenvalue problem

$$(A + Be^{-\lambda\tau})x = \lambda x, \tag{2.7}$$

where

$$A = \begin{pmatrix} -\mu_m - \frac{\sigma}{\theta} - \varphi_m & -\varphi_f & 0 \\ -\varphi_m & -\mu_f - \frac{\sigma}{\theta} - \varphi_f & 0 \\ \varphi_m & \varphi_f & -\mu_p - \frac{\sigma}{\theta} \end{pmatrix},$$

$$B = \begin{pmatrix} 0 & 0 & kS_m(\tau) \\ 0 & 0 & kS_f(\tau) \\ 0 & 0 & 0 \end{pmatrix}$$

and $\varphi_m = 2\rho\bar{f}^2/(\bar{m} + \bar{f})^2$, $\varphi_f = 2\rho\bar{m}^2/(\bar{m} + \bar{f})^2$. Using Hadeler's arguments [11], it follows that $\bar{\lambda}$ is not only an algebraically simple eigenvalue but also the eigenvalue with the largest real part. Hence, by Proposition 5 [11], the unique exponential solution $(\bar{m}, \bar{f}, \bar{p})e^{\bar{\lambda}t}$ is linearly stable (in the sense of stability of exponential solutions of homogeneous evolution equations).

When resistant parasite strains are introduced in a parasite population, the first question we ask is under what condition a resistant strain can invade in the population when the sensitive strain is already established (at the exponential solution). If the condition allows the resistant strain to invade, the next question we study is how drug treatment may affect the long term coexistence of both sensitive and resistant strains.

2.2. Invasion of resistant strains and coexistence

To explore the potential invasion of resistant strains in an environment mediated by chemotherapy (treatment) and resistance, we have to study the interaction of two strains. Introducing the time delay in Model (2.1) leads to the following two-strain model:

$$\begin{aligned} \dot{m}_i &= S_m(\tau)B_i(t-\tau) - \left(\mu_m + \frac{\sigma}{\theta_i}\right)m_i - \sum_{j=1}^{2}\varphi_{ij}(m,f), \\ \dot{f}_i &= S_f(\tau)B_i(t-\tau) - \left(\mu_f + \frac{\sigma}{\theta_i}\right)f_i - \sum_{j=1}^{2}\varphi_{ji}(m,f), \\ \dot{p}_{ij} &= \varphi_{ij}(m,f) - \left(\mu_p + \frac{\sigma}{\theta_i}\right)p_{ij}, \\ B_i(t-\tau) &= k_{ii}p_{ii}(t-\tau) + k_{12}p_{12}(t-\tau) + k_{21}p_{21}(t-\tau), \\ &\quad i,j = 1,2, \end{aligned} \tag{2.8}$$

where all variables and parameters have the same meanings as in Systems (2.1) and (2.2). In the following, we set $\theta_1 < \theta_2$.

In the absence of resistant strains, System (2.8) reduces to a subsystem like the one generated by System (2.2). The subsystem, from the prior analysis, has a unique positive exponential solution $(\bar{m}_1, \bar{f}_1, \bar{p}_{11})e^{\bar{\lambda}_1 t}$, which is locally stable with respect to the subsystem in the absence of resistant strains. If we let $E_1 = (\bar{m}_1, \bar{f}_1, \bar{p}_{11}, 0, 0, 0, 0, 0)$ then $E_1e^{\bar{\lambda}_1 t}$ is an exponential solution for System (2.8). When this solution is unstable it is expected that Strain 2 can invade and persist in the population if a small number of Strain 2 parasites are introduced.

For simplicity, we assume that $\mu_m = \mu_f = \mu_s$ (results will not vary if they are slightly different) and consider the stability of $E_1 = (1, 1, \bar{p}_{11}, 0, 0, 0, 0, 0)$, where $\bar{p}_{11} = 2\rho_{11}/(\bar{\lambda}_1 + \mu_p + \sigma/\theta_1)$. According to Hadeler [11], the stability of $E_1e^{\bar{\lambda}_1 t}$ is decided from the analysis of the following eigenvalue problem

$$(J_1 + J_2e^{-\lambda\tau})x = \lambda x, \tag{2.9}$$

where

$$J_1 = \begin{pmatrix} A_1 & * & * \\ 0 & A_2 & * \\ 0 & 0 & A_3 \end{pmatrix}, \quad J_2 = \begin{pmatrix} B_1 & * & * \\ 0 & B_2 & * \\ 0 & 0 & 0 \end{pmatrix},$$

$$A_2 = \begin{pmatrix} -\mu_m - \frac{\sigma}{\theta_2} - \rho_{21} & 0 & 0 & 0 \\ 0 & -\mu_f - \frac{\sigma}{\theta_2} - \rho_{12} & 0 & 0 \\ 0 & \rho_{12} & -\mu_p - \frac{\sigma}{\theta_1} & 0 \\ \rho_{21} & 0 & 0 & -\mu_p - \frac{\sigma}{\theta_2} \end{pmatrix},$$

$$B_2 = \begin{pmatrix} 0 & 0 & k_{12}S_m(\tau) & k_{21}S_m(\tau) \\ 0 & 0 & k_{12}S_f(\tau) & k_{21}S_f(\tau) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$A_3 = -\mu_p - \sigma/\theta_2$, and A_1, B_1 are equal to A, B in Eq. (2.7) with $\varphi_m = \varphi_f = \rho_{11}/2, k = k_{11}$ and $\theta = \theta_1$. The off-diago-

nal blocks $*$ are not of interest for a linear stability analysis. By Proposition 5 [11], $E_1e^{\bar{\lambda}_1 t}$ is linearly stable if for all eigenvalue λ of (2.9) (other than $\bar{\lambda}_1$) the real parts of $(\lambda-\bar{\lambda}_1)$ are negative, whereas it is unstable if there exists a λ such that $(\lambda-\bar{\lambda}_1)$ has a positive real part. The eigenvalues of (2.9) are given by $-\mu_p-\sigma/\theta_2$ and the roots of equations

$$\mathrm{Det}(A_1+B_1e^{-\lambda\tau}-\lambda I)=0, \tag{2.10}$$

$$\mathrm{Det}(A_2+B_2e^{-\lambda\tau}-\lambda I)=0. \tag{2.11}$$

By the former analysis, $\bar{\lambda}_1$ is the root with the largest real part of all roots of Eq. (2.10). Therefore, $E_1e^{\bar{\lambda}_1 t}$ is linearly stable if $\bar{\lambda}_1$ is greater than $-\mu_p-\sigma/\theta_2$ and all roots of Eq. (2.11).

In order to quantify these results we consider the case where $\rho_{12}=\rho_{21}=\rho$ and $S_m(\tau)=S_f(\tau)=S(\tau)$ in what follows. The roots of (2.11) are given by $-\mu_s-\rho-\sigma/\theta_2$ and the roots of the equation

$$\left(\lambda+\mu_p+\frac{\sigma}{\theta_2}\right)\left(\left(\lambda+\mu_p+\frac{\sigma}{\theta_1}\right)\left(\lambda+\mu_s+\rho+\frac{\sigma}{\theta_2}\right)-k_{12}\rho S(\tau)e^{-\lambda\tau}\right)=\rho k_{21}S(\tau)e^{-\lambda\tau}\left(\lambda+\mu_p+\frac{\sigma}{\theta_1}\right).$$

Rewriting the equation as

$$\lambda+\mu_s+\rho+\frac{\sigma}{\theta_2}-\frac{\rho k_{12}S(\tau)e^{-\lambda\tau}}{\lambda+\mu_p+\frac{\sigma}{\theta_1}}-\frac{\rho k_{21}S(\tau)e^{-\lambda\tau}}{\lambda+\mu_p+\frac{\sigma}{\theta_2}}=0, \tag{2.12}$$

and observing that the left side of (2.12) is a function of λ, $f(\lambda)$. As λ increases from $-\mu_p-\sigma/\theta_2$ to $+\infty$, $f(\lambda)$ strictly increases from $-\infty$ to $+\infty$. Thus there exists a number $\lambda_0>-\mu_p-\sigma/\theta_2$ such that $f(\lambda_0)=0$. If we define $D(\delta)=A_2+B_2\delta$ then λ_0 is actually an eigenvalue of the matrix $D(e^{-\lambda_0\tau})$, whose off-diagonal elements are nonnegative. The corresponding eigenvector is given by $\left(1,1,\frac{\rho}{\lambda_0+\mu_p+\sigma/\theta_1},\frac{\rho}{\lambda_0+\mu_p+\sigma/\theta_2}\right)$, which has positive components. Therefore, λ_0 is actually the principal eigenvalue of the matrix $D(e^{-\lambda_0\tau})$, i.e., the spectral bound $s(D(e^{-\lambda_0\tau}))$ is λ_0.

Now, assume that (2.11) has some root $\lambda=\alpha+\beta i$ with $\alpha,\beta\in\mathbb{R}$ and $\alpha>\lambda_0$. Then λ is an eigenvalue of the matrix $D(e^{-\lambda\tau})$ and $|e^{-\lambda\tau}|=e^{-\alpha\tau}<e^{-\lambda_0\tau}$. Therefore,

$$\alpha\leqslant s(D(e^{-\lambda\tau}))\leqslant s(D(e^{-\alpha\tau}))\leqslant s(D(e^{-\lambda_0\tau}))=\lambda_0,$$

a contradiction. It follows that the largest real part of roots of (2.11) is λ_0. Thus, to obtain the stability of $E_1e^{\bar{\lambda}_1 t}$, we only need to find the condition under which $\bar{\lambda}_1>\lambda_0$ (note that $\lambda_0>-\mu_p-\sigma/\theta_2>-\mu_s-\rho-\sigma/\theta_2$ since $\mu_s>\mu_p$).

Observe that $\bar{\lambda}_1$ is a root of Eq. (2.5) which can be rewritten as

$$g(\lambda)=\lambda+\mu_s+\rho_{11}+\frac{\sigma}{\theta_1}-\frac{\rho_{11}k_{11}S(\tau)e^{-\lambda\tau}}{\lambda+\mu_p+\frac{\sigma}{\theta_1}}=0.$$

Notice that $f(\bar{\lambda}_1)>0=g(\bar{\lambda}_1)$ is equivalent to the inequality

$$\rho+\frac{\sigma}{\theta_2}-\frac{\rho k_{12}S(\tau)e^{-\bar{\lambda}_1\tau}}{\bar{\lambda}_1+\mu_p+\frac{\sigma}{\theta_1}}-\frac{\rho k_{21}S(\tau)e^{-\bar{\lambda}_1\tau}}{\bar{\lambda}_1+\mu_p+\frac{\sigma}{\theta_2}}>\rho_{11}+\frac{\sigma}{\theta_1}-\frac{\rho_{11}k_{11}S(\tau)e^{-\bar{\lambda}_1\tau}}{\bar{\lambda}_1+\mu_p+\frac{\sigma}{\theta_1}}. \tag{2.13}$$

Since $f(\lambda_0)=0$, Inequality (2.13) implies that $f(\bar{\lambda}_1)>f(\lambda_0)$. Therefore, in the case of $\bar{\lambda}_1>-\mu_p-\sigma/\theta_2$ or equivalently

$$\bar{\lambda}_1+\mu_p+\sigma/\theta_2>0, \tag{2.14}$$

by the strict monotonicity of f in the interval $(-\mu_p-\sigma/\theta_2,+\infty)$, $\bar{\lambda}_1>\lambda_0$ if and only if Inequality (2.13) holds.

Therefore, $E_1e^{\bar{\lambda}_1 t}$ is linearly stable if both inequalities (2.13) and (2.14) hold. Reversal of one of the two inequalities leads to the instability of $E_1e^{\bar{\lambda}_1 t}$. In the case where $\tau=0$, these stability conditions are reduced to those found in [18].

Symmetrically, there exists an exponential solution $E_2e^{\bar{\lambda}_2 t}$ for System (2.8), which represents the case where only Strain 2 parasites exist in the population. Following the same analysis above, one can come to the conclusion that $E_2e^{\bar{\lambda}_2 t}$ is stable if there hold the Inequalities (2.13) and (2.14) with interchanged indices (1 by 2 and 2 by 1). If both exponential solutions $E_1e^{\bar{\lambda}_1 t}$ and $E_2e^{\bar{\lambda}_2 t}$ are unstable, an exponential solution representing coexistence of the two strains is expected to exist (the proof of the existence is similar to that in [18]).

3. Numerical simulations

This section confirms the results via numerical simulations. Parameter values are chosen according to the following assumptions: we set Strain 1 to be drug-sensitive ($\theta_1=1$) and Strain 2 to be drug-resistant ($\theta_2>1$); the costs associated with the evolution of drug-resistant strains of parasites translate into diminished reproduction and transmission; and it is assumed that the birth rates of pairs involving Strain 2 parasites are decreasing functions of $\theta_2: k_{12}=k_{21}=k_{11}/2\theta_2, k_{22}=k_{11}/\theta_2^2$. We further retain the assumption that $\mu_s=10\mu_p$, reflecting diminished survival experienced by unmated worms, and that $\rho_{11}=\rho_{22}=\rho_{12}=\rho_{21}=\rho$, assuming no bias in pair formation between strains. With respect to the life cycle of schistosomes, we set $(30+35)/365\leqslant\tau\leqslant(30+35+140)/365$ year, assuming that the life span of an infected snail is 170 days with a latent period of 30 days, and that the juvenile duration is 35 days. As in [9], we assume that after the latent period the number of cercariae released by snails decreases exponentially; a mated pair of schistosomes is responsible for 200–300 eggs per day; the probabilities that eggs get into water and infect a snail are small and on the order of 10^{-5} to 10^{-4}; and the per capita rate of infection of humans by one cercariae is also chosen to have similar values (estimated in [9]). An infected snail is assumed to release 500–750 cercaria per day for the first few days of production. Using these values we have $k_{11}S(\tau)=0.6e^{-0.001806}$

$*(\tau - 65/365) * 365$ for the sensitive strain. The death rate of pairs μ_p includes the natural death rates of human hosts and parasite pairs, and the disease-induced death rate of human hosts. We choose $\mu_p = 0.114$ and $\rho = 0.8$.

From the conditions for the stability of the exponential solution $E_1 e^{\bar{\lambda}_1 t}$, we identify the Inequalities (2.13) and (2.14) by the conditions $g_1(\tau) > 0$ and $g_2(\tau) > 0$, respectively. The effect of the time delay can be explored by looking at how these conditions may be affected when τ increases. If we choose (θ_2, σ) as bifurcation parameters with all other parameter values fixed, then the contour curves given by the conditions $g_1(\tau) = 0$ and $g_2(\tau) = 0$ (in the (θ_2, σ) plane) determine the stability region for the persistent solution $E_1 e^{\bar{\lambda}_1 t}$. For convenience we call the curve corresponding to $g_i(\tau) = 0$ the curve $g_i(\tau) = 0$. Fig. 2 shows the contour curves $g_1(\tau) = 0$ (solid curve) and $g_2(\tau) = 0$ (dashed curve) with $\theta_1 = 1$ for different values of τ. For each fixed τ (e.g., $\tau = 65/365, (65 + 60)/365$ and $(65 + 110)/365$), the condition $g_i(\tau) > 0$ represents the region in which all points (θ_2, σ) lie below the curve $g_i(\tau) = 0$ $(i = 1, 2)$.

For comparison purposes we include the curve obtained in the non-delay case $(\tau = 0)$. For the parameter values used in Fig. 2, the curve $g_2(\tau) = 0$ always lies above the curve $g_1(\tau) = 0$ for each fixed τ. In this case, $g_1(\tau) > 0$ implies $g_2(\tau) > 0$. Therefore, $E_1 e^{\bar{\lambda}_1 t}$ is stable for (θ_2, σ) below the curve $g_1(\tau) = 0$, and it is unstable above the curve in which case Strain 2 can invade.

We observe that, the curve $g_1(\tau) = 0$ gets lower as τ increases. This implies that the introduction of time delay makes it more likely for drug-resistant strains to invade and persist in a population. To see this more clearly, we can compare the threshold levels of resistance (θ_2) above which the resistant strain can invade for various values of time delay (τ) and for a fixed treatment rate (σ). For example, from Fig. 2 we see that for $\sigma = 0.3$, the threshold resistance level decreases from $\theta_2 \approx 3$ for $\tau = 0$ (the diamond) to $\theta_2 \approx 1.4$ for $\tau = 175/365$ (the astronaut). One possible explanation for the increased chance of invasion of the resistant strain is the following. Recall that the birth rate of sensitive strain is higher than that of resistant strain (e.g., $k_{22} = k_{11}/\theta_2^2$). Note that an increase in τ corresponds to a longer delay for generating new parasite, which can decrease the parasite reproduction. Thus, for a larger τ, the reduction will be less severe for the strain with a lower birth rate (which in this case is the resistant strain), suggesting that a larger τ will make it easier for the resistant strain to invade.

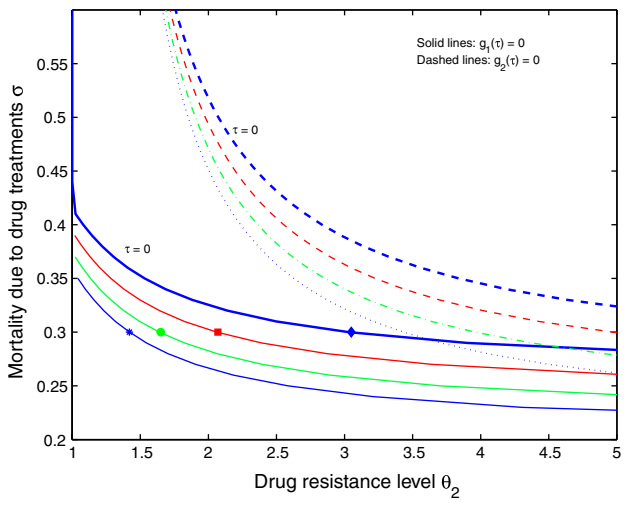

Fig. 2. Contour plots determined by $g_1(\tau) = 0$ (solid curves) and $g_2(\tau) = 0$ (dashed curves) for different values of τ. For each fixed τ, the persistent solution $E_1 e^{\bar{\lambda}_1 t}$ is stable for (θ_2, σ) below the curve $g_1(\tau) = 0$, and it is unstable above the curve in which case Strain 2 parasites can invade and persist. For each group of curves (solid or dashed), the corresponding values of τ (from top to bottom) are $\tau = 0$, $65/365, 125/365$ and $175/365$. The symbols (diamond, astronaut, etc.) represent the threshold resistance levels (for $\sigma = 0.3$ and various values of time delay τ) above which the resistant strains can invade and persist.

We can explore the influence of delay on different parasite strains by examining the composition of these strains in the population for different values of τ. Consider new variables, y_1 and y_2, which are scaled p_{11} and p_{22} and are defined as follows. Let $x(t)$ be the solution of System (2.8) with initial condition $x(0) = x_0$, and let

$$y(t) = \frac{x(t)}{\int_{-\tau}^{0} e^* \cdot x(t+s)ds},$$

where $e^* = (1, 1, \cdots, 1)$ is the row vector with all components equal to 1 and the dot "$\cdot$" denotes the inner product. Then the exponential solution $E_1 e^{\bar{\lambda}_1 t}$ changes into $\bar{\lambda}_1 E_1/(1 - e^{-\bar{\lambda}_1 \tau}) e^* \cdot E_1$. Note that p_{11} and p_{22} are components of x, and that the corresponding components of y, denoted by y_1 and y_2, represent the proportions of p_{11} and p_{22} in the total population. It can be verified that $p_{ii} \to 0$ if and only if $y_i \to 0$ as $t \to \infty$ $(i = 1, 2)$. Figs. 3 and 4 illustrate the time changes of y_1 and y_2 for two values of the delay, $\tau = 65/365$ and $175/365$. In Fig. 3, the point $(\theta_2, \sigma) = (3, 0.23)$ is chosen to be below the curve $g_1(175/365) = 0$ (see Fig. 2) and hence $E_1 e^{\bar{\lambda}_1 t}$ is stable for both values of τ. In this case, Strain 2 can not persist in the population (p_{22} and y_2 tend to 0 as $t \to \infty$). In Fig. 4, $(\theta_2, \sigma) = (3, 0.28)$ is above the curve $g_1(65/365) = 0$ and hence $E_1 e^{\bar{\lambda}_1 t}$ is unstable. In this case, both stains coexist.

4. Variable delays

In the previous sections, by introducing a fixed delay inspired by the life history of schistosomes into Model (2.1), we investigated the impact of the delay on the invasion and persistence of drug-resistant parasite strains as well as on multi-strain coexistence. In real systems, for different genotypes of schistosome parasites the life cycles may involve different time delays. Furthermore, the costs associated with the evolution of drug-resistant strains of schistosomes may not only translate into diminished reproduction and transmission, but also prolonged life cycles. That is, the delay τ in Model (2.8) associated with different genotypes of parasites may vary. Therefore, biologically it

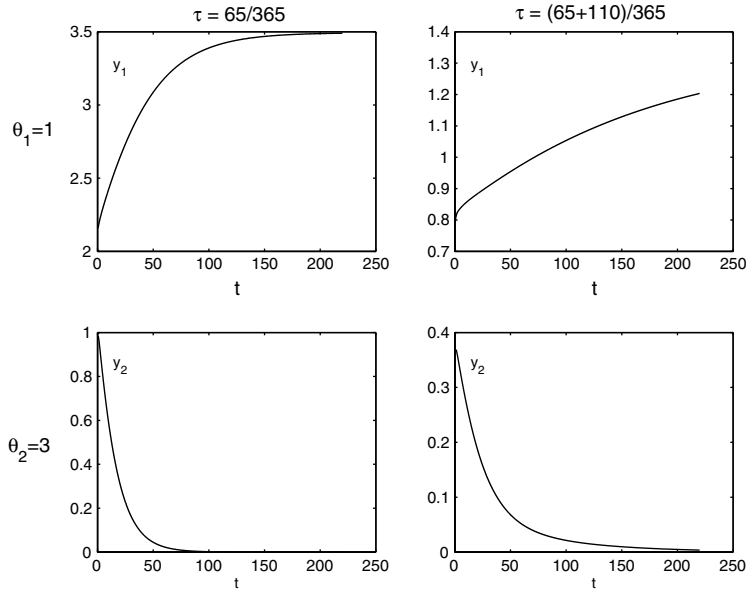

Fig. 3. Time plots of y_1 and y_2 (see text). The parameter values are chosen so that the point $(\theta_2, \sigma) = (3, 0.23)$ lies below the curve $g_1(175/365) = 0$ (see Fig. 2), for which $E_1 e^{\tilde{\lambda}_1 t}$ is stable when $\tau = 65/365, 175/365$. It is shown that Strain 2 parasites cannot invade.

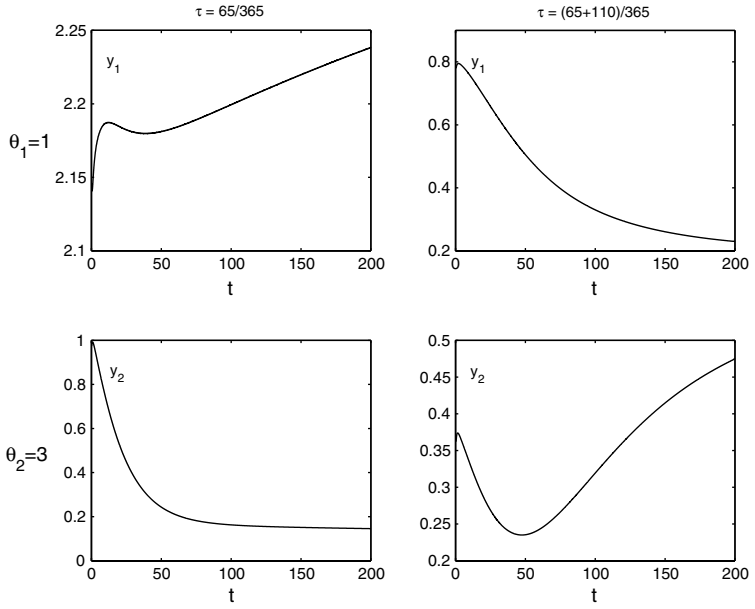

Fig. 4. Similar to Fig. 3 except that the parameter values are chosen such that $(\theta_2, \sigma) = (3, 0.28)$ is above the curve $g_1(65/365) = 0$, for which $E_1 e^{\tilde{\lambda}_1 t}$ is unstable for $\tau = 65/365$ and $175/365$. It is shown that Strain 2 parasites can invade into the population and coexist with Strain 1 parasites.

is interesting to examine the effect of variable delays on the invasion and coexistence conditions for drug-resistant strains of parasites.

Denote the time period of Strain i parasite's life cycle by τ_i. The delay τ_i may also be a function of the drug resistance level θ_i. Substituting τ_i for τ with τ_i in System (2.8), we get a system with different delays for different strains. Just as System (2.8), the new system is a homogeneous system, and has exponential solutions representing the scenario in which only one parasite strain is present. We use $\widetilde{E}_1 e^{\tilde{\lambda}_1 t}$ to denote the Strain 1 persistent solution, where $\tilde{\lambda}_1$ is the unique solution of Eq. (2.5) with the delay τ_1. The stability analysis is very similar to that of the original system (2.8). In fact, following the argument and assumption as in Section 2, one can show that $\widetilde{E}_1 e^{\tilde{\lambda}_1 t}$ is stable if

$$\rho + \frac{\sigma}{\theta_2} - \frac{\rho k_{12} S(\tau_2) e^{-\tilde{\lambda}_1 \tau_2}}{\tilde{\lambda}_1 + \mu_p + \frac{\sigma}{\theta_1}} - \frac{\rho k_{21} S(\tau_2) e^{-\tilde{\lambda}_1 \tau_2}}{\tilde{\lambda}_1 + \mu_p + \frac{\sigma}{\theta_2}} > \rho_{11} + \frac{\sigma}{\theta_1} - \frac{\rho_{11} k_{11} S(\tau_1) e^{-\tilde{\lambda}_1 \tau_1}}{\tilde{\lambda}_1 + \mu_p + \frac{\sigma}{\theta_1}} \tag{4.15}$$

and

$$\tilde{\lambda}_1 + \mu_p + \sigma/\theta_2 > 0. \tag{4.16}$$

Therefore, Strain 2 parasites can invade the population if one of the two inequalities is reversed.

To see the quantitative difference due to the variable delays introduced in Model (2.8), we numerically compare the stability condition (4.15) with Inequality (2.13) using the same parameter values chosen in Section 3. Let Strain 1 ($\theta_1 = 1$) denote the drug-sensitive strain and let Strain 2 ($\theta_2 > 1$) denote the drug-resistant strain. Furthermore, it is assumed that drug-resistant strains of parasites pay their costs associated with drug resistance in two respects: diminished reproduction and transmission, and prolonged life cycles. For the costs of prolonged life cycles, we set $\tau_2 = \tau_1 + \varepsilon_1(\theta_2 - 1)/(\theta_2 + \varepsilon_2)$, where $65/365 \leqslant \tau_1 \leqslant 175/365$. That is, the longest life cycle of Strain 2 parasites is equal to $\tau_1 + \varepsilon_1$. A biologically reasonable choice is that $\varepsilon_1 = 56/365$ and $\varepsilon_2 = 2$.

We identify Inequalities (4.15) and (4.16) by $G_1(\tau_1, \theta_2) > 0$ and $G_2(\tau_1) > 0$, respectively. Recall that $g_i(\tau) > 0$ ($i = 1, 2$) are the stability conditions for the exponential solution $E_1 e^{\tilde{\lambda}_1 t}$ of Model (2.8) with the fixed delay τ. Thus, if $\tau_1 = \tau$, then $G_2(\tau_1) = g_2(\tau)$. Hence, the only difference will be reflected by $g_1(\tau)$ and $G_1(\tau_1, \theta_2) > 0$. As in Fig. 2, we plot the curve $G_1(\tau_1, \theta_2) = 0$ for $\tau_1 = 65/365, 125/365$ and $175/365$. The curves are shown in Fig. 5, where the curves $g_1(\tau) = 0$ with $\tau = \tau_1$ are plotted as solid lines. The stable region (below the curve $G_1(\tau_1, \theta_2) = 0$) is slightly larger than that in the case of a fixed delay the region below the curve $g_i(\tau) = 0$, $i = 1, 2$. This suggests that the variable delay induced by drug resistance of parasites has a similar effect as the fixed delay on the invasion and persistence of drug-resistant strains. Of course, we can not rule out the possibility that a variable delay may generate significantly different outcomes if other complexities of the system are considered (for example, explicitly introducing state variables for parasite stages in the intermediate snail hosts or incorporating heterogeneous responses of snail hosts to different strains of parasites).

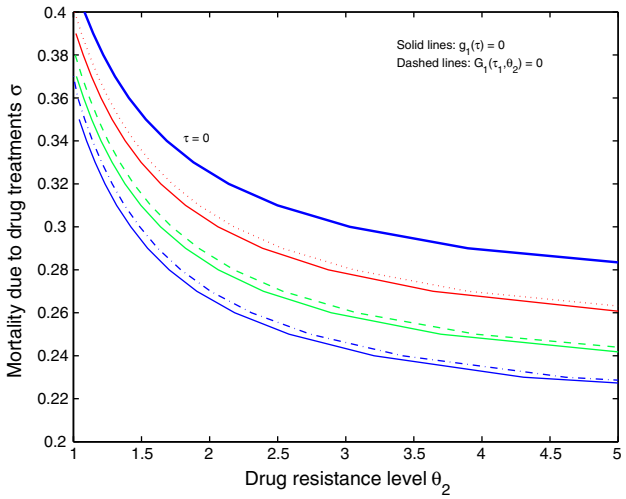

Fig. 5. Contour plots determined by $G_1(\tau_1, \theta_2) = 0$ showing the stability region of the persistent solution $\tilde{E}_1 e^{\tilde{\lambda}_1 t}$ for Model (2.8) with delays that vary with different drug resistance of parasites (dashed curves). The values of τ_1 are $65/365, 125/365$ and $175/365$ (from top to bottom). Resistant strains can invade for (θ_2, σ) above the curve for each fixed τ_1. For ease of comparison, the curves $g_1(\tau) = 0$ are also plotted for $\tau = \tau_1$ (solid).

5. Discussion

The desire to incorporate additional details into models is often strong particularly, in the presence of complex interactions like those associated with dynamics of schistosomiasis (Fig. 1). Here, we expanded our earlier work [18] to include not only the impact of the parasite's mating system but also the effect of life-history stages on schistosomiasis multi-strain coexistence. We apply Hadeler's results on the existence and stability of exponential solutions (for homogeneous systems) as well as his work on pair formation [11] to the study of schistosomiasis.

The conditions for the linear stability of exponential solutions that represent the presence of a single strain is derived, which are used to discuss the invasion and persistence of drug-resistant parasite strains. The trade-offs associated with the cost of resistance (diminished reproduction and prolonged life cycle) and selection (increased mortality of the wild type) are evaluated in a framework that considers (in a rather simple way) both the non-adult parasite and mating adults. What we have found is that the incorporation of additional complexity via the addition of a time delay and mating may have substantial quantitative influence on the likelihood of invasion and persistence of drug-resistant parasite stains, although the qualitative outcomes of the system are not affected dramatically (see Fig. 2). Consequently, when modeling host–parasite systems such as the one considered in this paper, depending on the focus of the study, the inclusion of time delay may be important in some cases, while in other cases a simple caricature of the life history of the parasite is enough.

Schistosome mating structure could be pretty complicated. Cosgrove and Southgate [6] demonstrated that one species can have the competitive advantages over another one in terms of a stronger homospecific mate preference and mating more easily with females of either species. It was also observed that single males of one species of schistosoma actively pull paired females away from their males [16,6]. It is interesting and valuable to investigate the possible effects of those phenomena on the evolution of drug-resistant strains of schistosoma.

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