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Biomath Forum

ORIGINAL ARTICLE

A novel multi-scale immuno-epidemiological model of visceral leishmaniasis in dogs

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Received: 8 August 2018, accepted: 2 January 2019, published: 23 January 2019

***Abstract*—Leishmaniasis is a neglected and emerging disease prevalent in Mediterranean and tropical climates. As such, the study and development of new models are of increasing importance. We introduce a new immuno-epidemiological model of visceral leishmaniasis in dogs. The within-host system is based on previously collected and published data, showing the movement and proliferation of the parasite in the skin and the bone-marrow, as well as the IgG response. The between-host system structures the infected individuals in time-since-infection and is of vector-host type. The within-host system has a parasite-free equilibrium and at least one endemic equilibrium, consistent with the fact that infected dogs do not recover without treatment. We compute the basic reproduction number $\mathscr{R}_0$ of the immuno-epidemiological model and provide the existence and stability results of the population-level disease-free equilibrium. Additionally, we prove existence of an unique endemic equilibrium when $\mathscr{R}_0 > 1$, and evidence of backward bifurcation and existence of multiple endemic equilibria when $\mathscr{R}_0 < 1$.**

***Keywords*-leishmaniasis in dogs, backward bifurcation, immuno-epidemiological model, stability, parameter estimation, immune dynamics**

AMS SUBJECT CLASSIFICATION: 92D30

I. INTRODUCTION

The leishmaniases are a group of diseases found in over 90 countries around the world, spread by over 30 species of the phlebotomine sand flies and infecting a variety of hosts including humans and dogs. While cutaneous leishmaniasis is more common, visceral leishmaniasis (VL) is lethal if untreated. We focus on zoonotic visceral leishmaniasis (ZVL), which has symptoms including enlarged spleen and liver and non-specific symptoms such as fever, weight loss, and anemia [1]. The non-specificity makes diagnosis challenging, particularly in the case of dogs [15]. The leishmaniases are classified as a Neglected Tropical Disease (NTD), with an estimated 0.2-0.4 million new human cases per year [14] and hundreds of millions at risk of new infection [19]. The WHO has stated that it is one of the most significant tropical diseases in the world [19]. As such, it is imperative to continue the study of VL, including its epidemiology, immunology, control measures, and identification.

Visceral leishmaniasis is usually caused by the *L. donovani* and *L. infantum* protozoa. The *L. donovani*-induced VL is more common in Africa

Citation: J. Shane Welker, Maia Martcheva, A novel multi-scale immuno-epidemiological model of visceral leishmaniasis in dogs, Biomath 8 (2019), 1901026, http://dx.doi.org/10.11145/j.biomath.2019.01.026

and Asia, while the *L. infantum*-induced VL is more common in the Americas and the Mediterranean [10]. While dogs and other mammals are infected by the *L. donovani*-induced VL, it has been shown that dogs are a primary reservoir only for the disease caused by the *L. infantum* species [2]. In fact, previous work has postulated that dogs are the main contributor to the spread of VL, claiming that 20% of the infected dogs cause 80% of transmission [2]. For these reasons, we focus primarily on the role of dogs in the persistence of VL.

To date, there have been few mathematical models for the between-host dynamics of VL [15]. Some models have chosen to compartmentalize asymptomatic or latently infected, resistant, and/or recovered classes, but almost all models have been ODEs. Some models, including the first model of VL in dogs by Dye includes resistance from birth [3]. Another model was developed by Ribas *et al* [4] which studies the population level dynamics between dogs and humans. The model was used to argue that treatment in dogs does not reduce significantly human illness. Shimozako *et al* considered a model of leishmaniasis in dogs and humans [16] and concluded that latent dogs contribute more to the illness than clinically ill dogs. Seva *et al* [12] investigated an outbreak of VL in Spain through a model that involved multiple host classes – rabbits, hares, dogs, and humans. All of the VL epidemic models studied to date are single-scale ODE models.

Even fewer models have been made for the within-host dynamics. Länger *et al* [8] developed a model examining the effect of IgG1, IgG2a, and lymphocytes on the parasite load, concluding that their model could be used in identifying biologically significant parameters [8]. Siewe *et al* [17] modeled macrophages, parasite loads, dendritic cells, T cells, and cytokines, and simulated the effects of various control measures. As a result, they stated that an increase in IFN-γ production should lead to a decrease in parasite load; an implication for potential therapy.

We develop, for the first time, an immuno-epidemiological model for VL. While still in the early stages of development, we intend for this model to display the effect that the within-host dynamics may have on infection of the vector. Additionally, we hope to assess the infectivity of a vector based on parasite reproduction and, eventually, control measure efficacy. Similarly, we plan to examine the parasite reproduction inside hosts with respect to the efficacy towards a vector, immune response, and treatment. Since these processes occur at a drastically different rate, we adopt the multi-scale approach.

Our within-host system was designed to fit data from Courtenay *et al* [2]. Our between-host system is of vector-host type, with the infected host class structured by time-since-infection. The between-host system contains susceptible, infected, and recovered host classes and susceptible, carrier, and infectious vector classes. Courtenay *et al* [2] conclude that, while samples were taken from both the skin tissue and bone marrow to record parasite loads, it is the parasite load in the skin tissue that is the most reliable indicator of VL infection [2]. We use this fact in the linking of the within- and between-host systems.

Following the introduction of the model in Section 2, we present a parasite-free equilibrium of the within-host system and prove it to be unstable in Section 3.1. Then, in Section 3.2, we introduce the basic reproduction number $\mathscr{R}_0$, and prove the disease-free equilibrium of the immuno-epidemiological model to be locally asymptotically stable when $\mathscr{R}_0 < 1$. We show the existence of an endemic equilibrium when $\mathscr{R}_0 > 1$, and the existence of multiple endemic equilibria and the presence of backward bifurcation, when $\mathscr{R}_0 < 1$. In Section 4 we discuss our conclusions.

II. The Model

A. The Within-Host System

Our within-host model is motivated by time series data in Courtenay *et al* [2] pertaining to the parasite loads in the skin tissue and bone marrow of dogs, as well as the immunoglobulin G (IgG) concentration. We derive a system coupling the

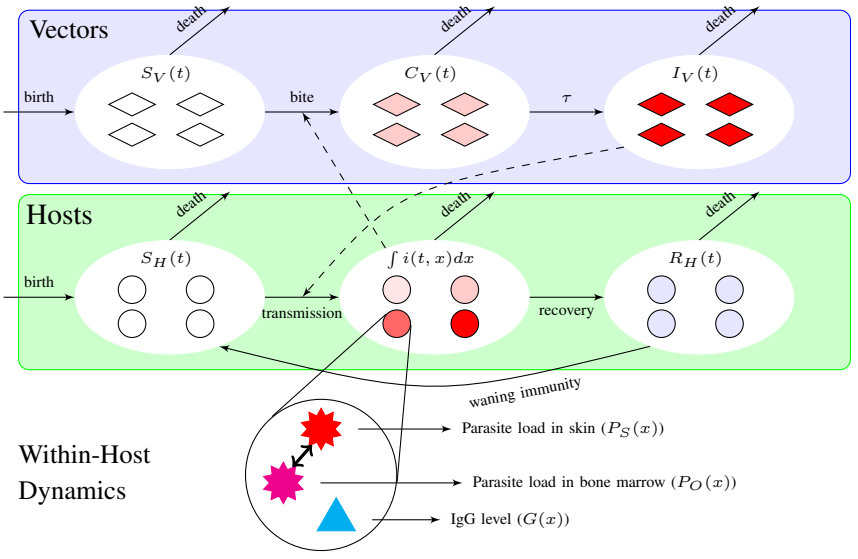


Fig. 1: The flow-chart of the immuno-epidemiological model of VL in dogs

dynamics of the parasite load in the skin tissue ($P_S(x)$), the parasite load in the bone marrow ($P_O(x)$), and the IgG concentration ($G(x)$), where x is the time-since-infection. The subscript S will indicate skin tissue, while the subscript O will indicate the bone marrow. We first introduce the model below and then we explain and motivate it. A full list of parameter meanings can be found in Table I and the variable meanings in Table IV:

$$P_S' = r_S P_S\left(1-\frac{P_S}{K_S}\right)+\frac{1}{\rho}k_O P_O - k_S P_S - \varepsilon_S P_S G \quad (1)$$

$$P_O' = r_O P_O\left(1-\frac{P_O}{K_O}\right)-k_O P_O + k_S\rho P_S - \varepsilon_O P_O G \quad (2)$$

$$G' = a_S\rho P_S + a_O P_O - dG \quad (3)$$

For the parasite loads, we assume reproduction is limited by a carrying capacities K_S and K_O. Hence the equations for P_S' and P_O' use logistic terms to model recruitment, with rates r_S and r_O.

We note that to infect a host, a sand fly must deposit parasites into the skin, when it takes a blood meal. Similarly, for a sand fly to become infected, it must take a blood meal from an infected host's skin. As there are parasites in the bone marrow, we can assume mobility of the parasite between the skin tissue and bone marrow. Hence our model contains "travel terms," with rates k_O and k_S and density conversion coefficient ρ. Thus, for every time within-host unit, a fraction of the parasites in the skin move to the bone marrow, and vice versa.

While not much is known about the parasite, we assume that the life span is short, and we include the natural death as part of the logistic term. However, we include the clearance of the parasite induced by the immune response as a separate term. Hence ε_S and ε_O are the IgG induced clearance rates of the parasite.

Lastly, we assume that the IgG response is caused by the presence of the foreign parasite, i.e., the basal level of IgG present before the introduction of the parasite is not counted towards G. As such, a_S and a_O are the IgG production rates caused by the parasite loads. We assume that the clearance rate is the only way IgG leave the system, which occurs at rate d.

Courtenay *et al* [2] obtained data for the parasite loads (PL) and IgG concentration. We present simulations of our within-host system. The behaviors

TABLE I: Parameters for the within-host system.

Parameter	Description	Unit
a_O	P_O induced IgG production rate	IgG AU / [parasites · time x]
a_S	P_S induced IgG production rate	IgG AU / [parasites · time x]
d	Natural clearance rate of IgG	1 / [time x]
ε_O	IgG induced P_O clearance	1 / [time x · IgG AU/mL]
ε_S	IgG induced P_S clearance	1 / [time x · IgG AU/mL]
K_O	Parasite carrying capacity in bone marrow	parasites/mL
K_S	Parasite carrying capacity in skin tissue	parasites/g
k_O	Parasite travel rate from bone marrow to skin tissue	1 / [time x]
k_S	Parasite travel rate from skin tissue to bone marrow	1 / [time x]
r_O	Parasite reproduction rate in bone marrow	1 / [time x]
r_S	Parasite reproduction rate in skin tissue	1 / [time x]
ρ	Conversion Coefficient	[g skin] / [mL bone marrow]

of these curves are similar to that of the data provided. The result of our simulation is given by the curves in Figures 2(A)-2(C). The parameter values for the simulation can be found in Table II.

B. The Between-Host System

Few models exist for the between-host dynamics of VL, and even fewer for zoonotic VL in dogs. Previous models have largely been ODE in structure. Some models included an asymptomatic or latently infected class [15]. However, obtaning data on infectious dogs is obstructed by the fact that identifying infectious dogs can be very difficult [13]. Since an infectious host is considered only infectious to the vector, the most reliable way to test for VL is through xenodiagnosis, a process in which a susceptible vector population bites a possibly infected host, and is then tested for the presence of the parasite [2].

However, xenodiagnosis is not always feasible or practical [2]. Since the symptoms of VL are non-specific, it is difficult to separate the latently infected dogs from the infectious dogs. In our multi-scale model, we structure the infectious hosts by time-since-infection, with the assumption that hosts are less infectious and less likely to display symptoms closer to when they first contract the parasite. The time-since-infection structure provides flexibility; allowing for fitting data given in different time units in the two different scales – the within-host and the between-host. We first introduce the system for the between-host dynamics of VL. Definitions of the parameters used can be found in Table III and definitions of the variables used in Table IV:

$$S_H' = \Lambda_H - \frac{\beta_H a S_H I_V}{N} - m_H S_H + \gamma R_H, \quad (4)$$

$$i_t + k_u i_x = -(\sigma(x) + \mu(x) + m_H) i(t,x), \quad (5)$$

$$k_u i(t,0) = \frac{\beta_H a S_H I_V}{N}, \quad (6)$$

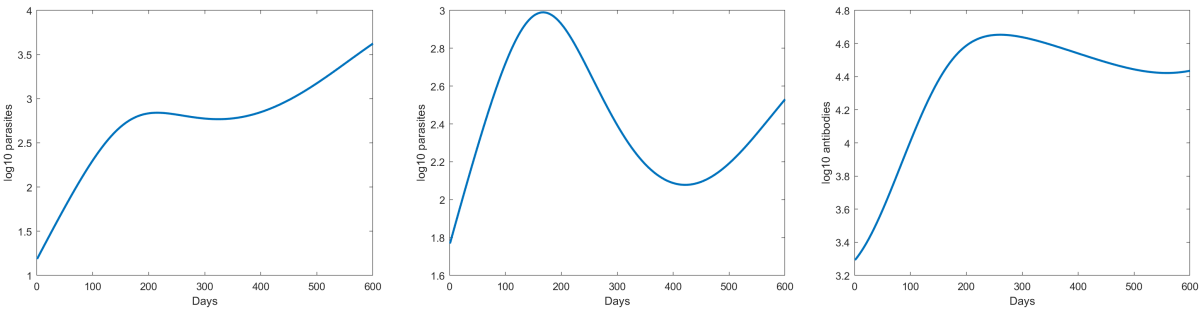
$$R_H' = \int_0^\infty \sigma(x) i(t,x) dx - (\gamma + m_H) R_H, \quad (7)$$

where x is the time-since-infection and the total number of infected hosts, $I_H(t)$, is

$$I_H(t) = \int_0^\infty i(t,x) dx. \quad (8)$$

The host system consists of susceptible $S_H(t)$, infected $i(t,x)$, and recovered/resistant $R_H(t)$ classes. The constant k_u in (5) and (6) accounts for the difference in the rates that the time t and time-since-infection x occur, i.e., $x = k_u t$. For the sake of initial analysis, we let $k_u = 1$. Susceptible hosts are born at rate Λ_H, and move to the infected class with standard incidence $\beta_H a S_H I_V / N$. Recovery takes place at rate σ. The integral term in (7) is the total number of recovered individuals per unit time. Hosts exit the system either through natural death, m_H, or disease-induced mortality, μ. The existence of relapse and reinfection shows the necessity of waning immunity at rate γ (see Table III).

The vector system consists of susceptible vectors $S_V(t)$, carrier vectors $C_V(t)$, who are infected



(a) (b) (c)

Fig. 2: Figures (a) and (b) show simulations of the parasites in the skin and bone marrow, respectively, in $\log_{10}$ values. Figure (c) shows simulations of $\log_{10}$ IgG antibody units.

TABLE II: Parameter values used.

Parameter	Value	Unit
a_O	4.550060×10^{-1}	IgG AU / [parasites · day]
a_S	1.739817×10^{-5}	IgG AU / [parasites · day]
d	4.136157×10^{-3}	parasites/day
ε_O	8.927579×10^{-7}	1 / [day · IgG AU/mL]
ε_S	6.968101×10^{-7}	1 / [day · IgG AU/mL]
K_O	1.034155×10^{6}	parasites/mL
K_S	1.007303×10^{8}	parasites/g
k_O	5.723339×10^{-9}	1 / day
k_S	5.228469×10^{-4}	1 / day
r_O	2.614700×10^{-2}	1 / day
r_S	2.965272×10^{-2}	1 / day
ρ	1	[g skin] / [mL bone marrow]

TABLE III: Parameters for the between-host system.

Parameter	Description	Units
a	Average biting rate	bites / [time t · vectors]
β_H	Rate of host becoming infected after bite	1 / [bites/hosts]
β_V	Rate of vector becoming infected after bite	1 / [bites/vectors]
γ	Rate of becoming susceptible after recovery	1 / [time t]
k_u	Time scaling constant	[time x] / [time t]
Λ_H	Birth rate of hosts	hosts / [time t]
Λ_V	Birth rate of vectors	vectors / [time t]
m_H	Natural death rate of hosts	1 / [time t]
m_V	Natural death rate of vectors	1 / [time t]
$\mu(x)$	Disease induced death rate of hosts	1 / [time t]
$\sigma(x)$	Rate of recovery of hosts	1 / [time t]
τ	Rate of moving from carrier to infectious	1 / [time t]

TABLE IV: Definitions of dependent variables.

Variable	Description	Unit
$S_H(t)$	Susceptible hosts at time t	hosts
$I_H(t)$	Infected hosts at time t	hosts
$i(t,x)$	Density of hosts infected x time units ago at time t	hosts / [time x]
$R_H(t)$	Recovered hosts at time t	hosts
$S_V(t)$	Susceptible vectors at time t	vectors
$C_V(t)$	Carrier vectors at time t	vectors
$N(t)$	Host population	hosts
$I_V(t)$	Infectious vectors at time t	vectors
$P_O(x)$	Parasite load of bone marrow at time x	parasites/mL
$P_S(x)$	Parasite load of skin tissue at time x	parasites/g
$G(x)$	IgG concentration at time x	IgG AU/mL

TABLE V: Parameters for linking.

Parameter	Description	Unit
ξ	Rate of exponential decay	1 / [parasites/g]
c_V	Maximal transmission coefficient	1 / [bites/vector]
δ_0	Constant	1 / mL
κ	Constant	1 / [IgG AU/mL $\cdot$ time t]
η	Constant	1 / [IgG AU/mL $\cdot$ time t]
ν	Constant	(unitless)
ψ_O	Constant	1 / [parasites/mL $\cdot$ time t]
ψ_S	Constant	1 / [parasites/g $\cdot$ time t]
θ_O	Constant	1 / parasites
θ_S	Constant	1 / parasites

but not infectious yet, and infectious vectors $I_V(t)$. While there are many unknowns about the sand flies and leishmania, it is known that the parasite must make its way through the sand fly after a blood meal before it can be deposited in a host. The time elapsed for the parasite to potentially infect a new host, called extrinsic incubation period, is comparable to the life span of the sand fly. This requires the carrier class for the vector.

$$S_V' = \Lambda_V - m_V S_V - \frac{aS_V}{N}\int_0^\infty \beta_V(x) i(t,x)dx \quad (9)$$

$$C_V' = \frac{aS_V}{N}\int_0^\infty \beta_V(x) i(t,x)dx - (\tau + m_V)C_V \quad (10)$$

$$I_V' = \tau C_V - m_V I_V, \quad (11)$$

Vectors are born at rate Λ_V, and exit the system only through natural death rate m_V. Vectors move from the carrier class to the infectious class at rate τ. The integral terms in (9) and (10) represent the force of infection of humans to susceptible vectors.

Since the rate of infection (ROI) is assumed to be dependent on x, the rate of recovery of hosts, σ, the disease-induced death rate of hosts, μ, and the rate of an infected host infecting a susceptible vector at the time of the blood meal, β_V, are also dependent on x.

C. Linking the Within- and Between-Host Systems

While much analysis is left, we note the different time scales that will be utilized. That of the parasites and vectors will occur much faster than that of the hosts. We introduce the methods in which we initially plan to incorporate the faster time scale into the spread of the virus.

Since Courtenay *et al* [2] concluded that the parasite load in the dog skin tissue was the best indicator of infectiousness to the vector, we use $P_S(x)$ to determine the rate of transmission $\beta_V(x)$:

$$\beta_V(x) = c_V e^{-\xi P_S^\nu(x)}, \quad (12)$$

where ξ is the rate of exponential decay, c_V is the maximal transmission coefficient, and ν =

$-2/\ln(10)$. This relationship was derived by Li *et al* [9], using data for dengue.

Assuming treatment, the recovery rate also depends on the time-since-infection. We assume recovery occurs when the within-host parasite load becomes zero. Thus, we let

$$\sigma(x) = \frac{\kappa G}{\delta_0 + \theta_S \rho P_S + \theta_O P_O}, \tag{13}$$

where δ_0 is a small constant, and θ_S, θ_O, and κ are constants [18]. Note that when P_S and P_O approach 0, σ becomes large due to δ_0.

To link the disease-induced mortality, μ, we let

$$\mu(x) = \psi_S \rho P_S + \psi_O P_O + \eta G, \tag{14}$$

where ψ_S, ψ_O, and η are constants, [6].

III. Analysis

A. Analysis of the Within-Host System

The within-host system (1)-(3) has a parasite-free equilibrium $\mathcal{E}_0 = (0, 0, 0)$. To determine its stability, we consider the Jacobian at the parasite-free equilibrium. We have the following result.

Theorem 1. The parasite-free equilibrium $\mathcal{E}_0$ is always unstable.

Proof: Let $\hat{k}_O = \frac{1}{\rho} k_O$, $\hat{k}_S = k_S \rho$, and $\hat{a}_S = a_S \rho$. The Jacobian of the within-host system evaluated at $\mathcal{E}_0$ is

$$J_0 := \begin{pmatrix} r_S - k_S & \hat{k}_O & 0 \\ \hat{k}_S & r_O - k_O & 0 \\ \hat{a}_S & a_O & -d \end{pmatrix},$$

which has the eigenvalue $\lambda_1 = -d$. The remaining eigenvalues are eigenvalues of the submatrix

$$J_1 := \begin{pmatrix} r_S - k_S & \hat{k}_O \\ \hat{k}_S & r_O - k_O \end{pmatrix}.$$

Note that $\hat{k}_O \hat{k}_S = k_O k_S$. Then $\mathcal{E}_0$ is stable if and only if $\det(J_1) = (r_S - k_S)(r_O - k_O) - k_S k_O > 0$ and $\mathrm{Tr}(J_1) < 0$. Suppose that $\det(J_1) > 0$. Note that

$$\begin{aligned} \det(J_1) &= r_S r_O - r_S k_O - r_O k_S \\ &= r_S(r_O - k_O) - r_O k_S. \end{aligned}$$

So $r_S(r_O - k_O) - r_O k_S > 0$ if and only if $r_S(r_O - k_O) > r_O k_S$. Then $r_O > k_O$. Similarly, we can get $r_S > k_S$. Hence $\mathrm{Tr}(J_1) > 0$ when $\det(J_1) > 0$. Therefore $\mathcal{E}_0$ is unstable. ■

This stability result heuristically makes sense as, without the introduction of treatment, infected hosts stay infected.

Theorem 2. The within-host system (1)-(3) always has at least one parasite equilibrium $\mathcal{E}^*$. This equilibrium is unique if $r_S < k_S$. If $r_S > k_S$, the equilibrium is unique if

$$\hat{k}_O \left(\frac{\varepsilon_S}{d} \hat{a}_S + \frac{r_S}{K_S} \right) > (r_S - k_S) \frac{\varepsilon_S}{d} a_O \tag{15}$$

Proof: To show existence, we set the within-host system equal to zero and reduce the system to

$$\begin{aligned} 0 =& r_S P_S \left(1 - \frac{P_S}{K_S}\right) + \hat{k}_O P_O - k_S P_S \\ & - \frac{\varepsilon_S}{d} P_S (\hat{a}_S P_S + a_O P_O) \end{aligned} \tag{16}$$

$$\begin{aligned} 0 =& r_O P_O \left(1 - \frac{P_O}{K_O}\right) - k_O P_O + \hat{k}_S P_S \\ & - \frac{\varepsilon_O}{d} P_O (\hat{a}_S P_S + a_O P_O). \end{aligned} \tag{17}$$

Solving (16) for P_O, we obtain $P_O = P_S f_1(P_S)$, where

$$f_1(P_S) = \frac{1}{\Phi_O(P_S)} \left[k_S + \frac{\varepsilon_S}{d} \hat{a}_S P_S - r_S \left(1 - \frac{P_S}{K_S}\right) \right]$$

and

$$\Phi_O(P_S) = \hat{k}_O - \frac{\varepsilon_S}{d} a_O P_S.$$

Substituting P_O in (17), we obtain the following equation for P_S:

$$F(P_S) := f_1(P_S) G_1(P_S) = 0$$

with

$$\begin{aligned} G_1(P_S) =& r_O \left(1 - \frac{P_S f_1(P_S)}{K_S}\right) - k_O + \frac{\hat{k}_S}{f_1(P_S)} \\ & - \frac{\varepsilon_O}{d} (\hat{a}_S P_S + a_O P_S f_1(P_S)). \end{aligned}$$

Denote by $\hat{P}_S$ the value of P_S such that $\Phi_O(\hat{P}_S) = 0$. Further, denote by $\bar{P}_S$ the value of P_S such that $f_1(\bar{P}_S) = 0$. We have

$$\bar{P}_S = \frac{r_S - k_S}{\frac{\varepsilon_S \hat{a}_S}{d} + \frac{r_S}{K_S}},$$

$$\hat{P}_S = \frac{\hat{k}_O}{\frac{\varepsilon_S}{d} a_O}.$$

We consider the following cases

Case 1:] We have $r_S < k_S$ or $r_O < k_O$. Then, $f_1(P_S) > 0$ and $\Phi_O(P_S) > 0$ iff $P_S \in (0, \hat{P}_S)$. We have that $f_1(P_S)$ is an incrasing function of P_S. Further $G_1(P_S)$ is a decreasing function of P_S. As $f_1(P_S) > 0$ on $P_S \in (0, \hat{P}_S)$ the roots of $F(P_S) = 0$ are the same as the roots of $G_1(P_S) = 0$. Since G_1 is decreasing, if a root exists, it must be unique. Since

$$G_1(0) = r_O - k_O + \frac{k_S k_O}{k_S - r_S} = r_O + \frac{k_O r_S}{k_S - r_S} > 0$$

if $k_S > r_S$, as in this case. On the other hand

$$\lim_{P_S \to \hat{P}_S^-} G_1(P_S) = -\infty$$

Since $G_1(P_S)$ is continuous on $(0, \hat{P}_S)$, then there is at least one solution of $G_1(P_S) = 0$. Hence, there exists a unique $P_S^* \in (0, \hat{P}_S)$ such that $F(P_S^*) = 0$ and $P_O^* = P_S^* f_1(P_S^*) > 0$. In this case, it is easy to see that

$$G^* = \frac{\hat{a}_S P_S^* + a_O P_O^*}{d}$$

is positive as well.

Case 2: We have $r_S > k_S$. Since $f_1(0) < 0$, the solution, if it exists, lies in a different interval. Note $f_1(P_S) > 0$ iff $P_S \in (\bar{P}_S, \hat{P}_S)$. However, in this case we don't know whether $\bar{P}_S < \hat{P}_S$ or vice versa. So we have to consider two subcases.

Case 2A: Assume inequality (15), that is, assume $\bar{P}_S < \hat{P}_S$. Then $f_1(P_S)$ is an increasing function of P_S with

$$f_1(\bar{P}_S) = 0, \qquad \lim_{P_S \to \hat{P}_S^-} f_1(P_S) = \infty.$$

It is easy to see that in this case we also have

$$\lim_{P_S \to \bar{P}_S^+} G_1(P_S) = \infty,$$
$$\lim_{P_S \to \hat{P}_S^-} G_1(P_S) = -\infty.$$

Further, $G_1(P_S)$ is also monotone and continuous as in Case 1. Hence, there exists a unique $P_S^* \in (\bar{P}_S, \hat{P}_S)$ such that $F(P_S^*) = 0$ and $P_O^* = P_S^* f_1(P_S^*) > 0$. In this case it is easy to see that G^* is positive as well. We also note that $F(\bar{P}_S) = \hat{k}_S > 0$. Thus, $\bar{P}_S$ is not a solution.

Case 2B: Assume $\bar{P}_S > \hat{P}_S$. Then $f_1(P_S)$ is a decreasing function of P_S.

$$f_1(\bar{P}_S) = 0, \qquad \lim_{P_S \to \hat{P}_S^-} f_1(P_S) = \infty$$

It is easy to see that in this case we also have

$$\lim_{P_S \to \bar{P}_S^+} G_1(P_S) = \infty,$$
$$\lim_{P_S \to \hat{P}_S^-} G_1(P_S) = -\infty.$$

Since $G_1(P_S)$ is also continuous as in Case 1, there exists at least one solution in $(\hat{P}_S, \bar{P}_S)$. However, in this case $G_1(P_S)$ may not be monotone and the equilibrium may not be unique. Hence, there exists at least one $P_S^* \in (\hat{P}_S, \bar{P}_S)$ such that $F(P_S^*) = 0$ and $P_O^* = P_S^* f_1(P_S^*) > 0$. In this case it is easy to see that G^* is positive as well, and $\bar{P}_S$ is not a solution to $F(P_S) = 0$.

■

B. Analysis of the Full Immuno-Epidemiological Model

The immuno-epidemiological model has a disease-free equilibrium

$$\mathscr{E}_0 = \left(\frac{\Lambda_H}{m_H}, 0, 0, \frac{\Lambda_V}{m_V}, 0, 0 \right). \tag{18}$$

We linearize model (4)-(11) around $\mathscr{E}_0$. Looking for exponential solutions of the form $\vec{z}(t) = \overline{z} e^{\lambda t}$,

we obtain the characteristic equation $F(\lambda) = 1$, where $\lambda \in \mathbb{C}$ and

$$F(\lambda) = \frac{\tau}{m_V + \lambda} \cdot \frac{am}{\tau + m_V + \lambda} \beta_H a \cdot \int_0^\infty \beta_V(x) e^{-\lambda x} e^{-\int_0^x (\sigma(\xi)+\mu(\xi)+m_H)d\xi} dx. \quad (19)$$

Then the basic reproduction number is $F(0)$, or

$$\mathscr{R}_0 = \underbrace{\overbrace{\frac{\tau}{\tau + m_V}}^{\substack{\% \text{ of vectors} \\ \text{that become} \\ \text{infectious}}} \cdot \frac{a\beta_H}{m_V}}_{\mathscr{R}_V} \cdot \overbrace{am \int_0^\infty \beta_V(x) e^{-\int_0^x (\sigma(\xi)+\mu(\xi)+m_H)d\xi} dx}^{\mathscr{R}_H}, \quad (20)$$

where $\mathscr{R}_V$ is the basic reproduction number of the vectors and $\mathscr{R}_H$ is the basic reproduction number of the hosts [11]. The parameter m denotes the ratio of the vector to hosts and is defined as

$$m = \frac{\Lambda_V}{m_V} \frac{m_H}{\Lambda_H}.$$

It should be noted that $\mathscr{R}_0$ is dependent on the within-host system.

Theorem 3. If $\mathscr{R}_0 < 1$, then the disease-free equilibrium $\mathscr{E}_0$ is locally asymptotically stable. If $\mathscr{R}_0 > 1$, then $\mathscr{E}_0$ is unstable.

Proof: Suppose $\mathscr{R}_0 < 1$. Then $F(\lambda) = 1$ has a unique negative solution $\lambda^* \in \mathbb{R}$. For a complex λ, let $\lambda = \alpha_1 + i\alpha_2$, and assume $\alpha_1 \geq 0$. Then

$$\begin{aligned} |F(\lambda)| \leq & \frac{a^2 \beta_H m \tau}{|m_V + \lambda| \, |\tau + m_V + \lambda|} \cdot \int_0^\infty \beta_V(x) \left| e^{-\lambda x} \right| \pi(x) dx \\ \leq & \frac{a^2 \beta_H m \tau}{(m_V + \alpha_1)(\tau + m_V + \alpha_1)} \cdot \int_0^\infty \beta_V(x) e^{-\alpha_1 x} \pi(x) dx \\ = & F(\alpha_1) \leq F(0) = \mathscr{R}_0 < 1. \end{aligned}$$

Since $1 = |F(\lambda)| \leq \mathscr{R}_0 < 1$, a contradiction, we must have $\alpha_1 < 0$. Hence every complex solution to $F(\lambda) = 1$ must have a negative real part. Therefore, $\mathscr{E}_0$ is locally asymptotically stable when $\mathscr{R}_0 < 1$.

Now suppose that $\mathscr{R}_0 > 1$. Then for positive $\lambda \in \mathbb{R}$,

$$\begin{aligned} F'(\lambda) = & \frac{(m_V + \lambda)(\tau + m_V + \lambda)(a^2 \beta_H m \tau)}{(m_V + \lambda)^2 (\tau + m_V + \lambda)^2} \cdot \int_0^\infty (-x) \beta_V(x) e^{-\lambda x} \pi(x) dx \\ & - \frac{a^2 \beta_H m \tau (\tau + 2m_V + 2\lambda)}{(m_V + \lambda)^2 (\tau + m_V + \lambda)^2} \cdot \int_0^\infty \beta_V(x) e^{-\lambda x} \pi(x) dx \\ = & - \frac{a^2 \beta_H m \tau}{(m_V + \lambda)^2 (\tau + m_V + \lambda)^2} \cdot \Bigg[(m_V + \lambda)(\tau + m_V + \lambda) \cdot \int_0^\infty x \beta_V(x) e^{-\lambda x} \pi(x) dx \\ & + (\tau + 2m_V + 2\lambda) \int_0^\infty \beta_V(x) e^{-\lambda x} \pi(x) dx \Bigg] \\ < & \, 0, \end{aligned}$$

since the bracketed expression is always positive for non-negative $\beta_V(x) \not\equiv 0$. Since $\mathscr{R}_0 > 1$, then $F(0) > 1$. Since

$$\lim_{\lambda \to \infty} F(\lambda) = 0$$

and F is decreasing, $F(\lambda) = 1$ has a unique positive solution $\lambda^* \in \mathbb{R}$. Thus $\mathscr{E}_0$ is unstable. ■

To study existence of endemic equilibria, we set the time derivatives in the between-host system equal to zero and reduce the system to

$$0 = \Lambda_H - \frac{\beta_H a S_H I_V}{N} - m_H S_H + \frac{\gamma}{\gamma + m_H} \cdot \frac{\beta_H a S_H I_V}{N} \Sigma, \quad (21)$$

$$\frac{f_{S_V}(I_V) S_H}{N^2} = Q, \quad (22)$$

$$N^2 - \frac{\Lambda_H}{m_H} N = - \frac{\beta_H a S_H I_V}{m_H} M, \quad (23)$$

where

$$f_{S_V}(I_V) := S_V = \frac{\Lambda_V}{m_V} - \frac{\tau + m_V}{\tau} I_V,$$
$$Q = \frac{(\tau + m_V)m_V}{\tau} \cdot \frac{1}{\beta_H a^2 B_V},$$
$$M = \int_0^\infty \mu(x)\pi(x)dx,$$
$$\Sigma = \int_0^\infty \sigma(x)\pi(x)dx,$$
$$B_V = \int_0^\infty \beta_V(x)\pi(x)dx,$$
$$\pi(x) = \exp\left(-\int_0^x (\sigma(\xi) + \mu(\xi) + m_H)d\xi\right),$$
$$N = S_H + \int_0^\infty i(t,x)dx + R_H$$
$$= \frac{\Lambda_H}{m_H} - \frac{\beta_H a S_H I_V}{N} M.$$

Solving (21) for S_H gives $f_{S_H}(I_V/N)$. Substituting that into (23) yields

$$N = \frac{\Lambda_H}{m_H} - \frac{\beta_H a \left[f_{S_H}\left(\frac{I_V}{N}\right)\right] \frac{I_V}{N}}{m_H} M =: f_N(I_V/N).$$

We let $X = \beta_H a I_V/N$ and $p = 1-\gamma\Sigma/(\gamma+m_H)$. We redefine f_{S_H} and f_N as functions of X, and obtain

$$f_{S_H}(X) = \frac{\Lambda_H}{m_H + pX},$$
$$f_N(X) = \frac{\Lambda_H}{m_H}\left[1 - \frac{MX}{m_H + pX}\right].$$

We have that

$$QN = S_V S_H/N = f_{S_V}(X) f_{S_H}(x)/f_N(X).$$

Expanding and rearranging, we obtain

$$a_0 X^2 + b_0 X + c_0 = 0, \tag{24}$$

where

$$a_0 = \frac{(p-M)^2}{m_H}\frac{m}{\mathscr{R}_0} + \frac{\tau + m_V}{\tau \beta_H a}(p - M), \tag{25}$$
$$b_0 = \frac{2m}{\mathscr{R}_0}(p - M) - mp + \frac{\tau + m_V}{\tau \beta_H a} m_H, \tag{26}$$
$$c_0 = \left(\frac{1}{\mathscr{R}_0} - 1\right) m_H m, \tag{27}$$

and $m = S_V^0/N^0$.

Theorem 4. When $\mathscr{R}_0 > 1$, there exists a unique positive endemic equilibrium.

Proof: We have that $a_0 > 0$, since $p - M > 0$. If $\mathscr{R}_0 > 1$, then c_0 is necessarily negative. Hence, the equation (24) has exactly one positive solution. It is not hard to see that in this case $S_H = f_{S_H}(X) > 0$ and $N = f_N(X) > 0$. This also implies that $S_V > 0$. Hence, a unique positive equilibrium exists. ■

On the other hand, if $\mathscr{R}_0 < 1$, (24) may have two positive soluitons or no positive solutions. Two positive solutions are obtained if equation (24) exhibits backward bifurcation. We find a necessary and sufficient condition for the existence of two equilibria:

$$p + aB_V m_H < 2M,$$

noting that M is the disease-induced mortality. Thus, backward bifurcation in this model can occur only if $M > 0$.

Theorem 5. If $\mathscr{R}_0 < 1$ and b_0 is negative, then backward bifurcation occurs and two endemic equilibria exist. If $\mathscr{R}_0 < 1$ and b_0 is positive, there are no endemic equilibria.

The existence of the two endemic equilibria is established by the backward bifurcation shown in Figure 3 where X is plotted on the y-axis and $\mathscr{R}_0$ is plotted on the x axis. The parameter varied in the figure is the mortality rate of the vector m_V. It may be important to note the decrease in the level of the upper equilibrium upon increasing m_V. This could imply that a stronger control measure on the vector could greatly affect the level of persistence of the disease.

IV. Discussion and Conclusion

In this paper, we present a new immuno-epidemiological model for zoonotic visceral leishmaniasis (ZVL) in dogs, in which the within-host model simulated infectiousness based on parasite load and the between-host model was structured by time-since-infection.

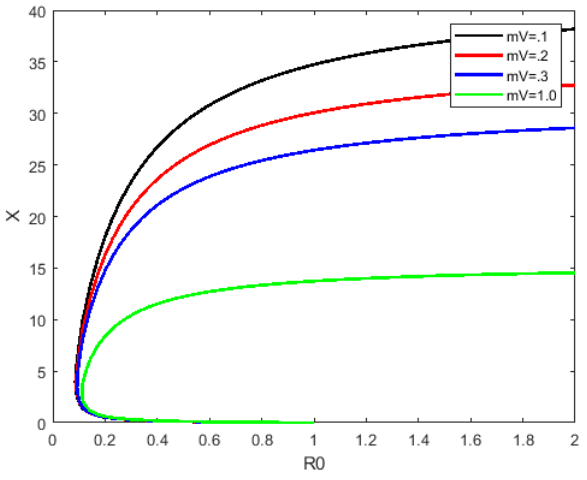


Fig. 3: Backward bifurcation of (24) when $\mathscr{R}_0 < 1$ and $b_0 < 0$. Various values of m_V are shown.

The within-host system examined the parasite loads in the skin and bone marrow, as well as the IgG concentration. This system agrees well with data provided by Courtenay *et al* [2]. The within-host model was shown to have an unstable parasite-free equilibrium, in which the parasite population dies out within the host. This equilibrium's stability is in the absence of treatment, consistent with the persistence of ZVL without treatment.

While the agreement of the model solutions with the data was satisfactory, in future work we will fit the model to the data and examine the biological significance of the values found for the parameters. Upon establishing the existence of equilibria and their stability, it is of great importance to examine the effect of control measures on the parasite population, as originally presented by Dye [3]. This would include existing medicinal treatments, a hypothetical vaccine, and control measures directly affecting the vector.

The basic reproduction number for the immuno-epidemiological model $\mathscr{R}_0$ was introduced, and the disease-free equilibrium of the between-host system was shown to be locally asymptotically stable when $\mathscr{R}_0 < 1$. We then derived a quadratic equation for the equilibria of the full system, based on a reduction of the system. This equation in $X := \beta_H a I_V/N$ was used to establish the existence and characterize the endemic equilibria of the immuno-epidemiological model. When $\mathscr{R}_0 > 1$, the model was shown to have a unique positive endemic equilibrium. However, when $\mathscr{R}_0 < 1$ and the coefficient of the linear term of the quadratic equation was negative, the presence of disease-induced mortality allowed for backward bifurcation to occur, consistent with the results found in ODE cases [5]. This provided justification for the existence of two endemic equilibria. The presence of subthreshold equilibria generally obstructs disease eradication. Control measures in this case should be directed towards (A) removing the cause of the backward bifurcation which in this case is the disease-induced mortality in dogs or (B) coupling sustain control measures that bring $\mathscr{R}_0$ below one with temporary control measures, such as mosquito spraying, to put the disease on elimination path [7].

Acknowledgements

The authors acknowledge partial support from NSF grant DMS-1515661, and the contributions of George Pu in the fitting of the within-host model. We also thank the referees for their comments and suggestions.

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