The role of adaptations in two-strain competition for sylvatic Trypanosoma cruzi transmission†

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This study presents a continuous-time model for the sylvatic transmission dynamics of two strains of Trypanosoma cruzi enzootic in North America, in order to study the role that adaptations of each strain to distinct modes of transmission (classical stercorarian transmission on the one hand, and vertical and oral transmission on the other) may play in the competition between the two strains. A deterministic model incorporating contact process saturation predicts competitive exclusion, and reproductive numbers for the infection provide a framework for evaluating the competition in terms of adaptive trade-off between distinct transmission modes. Results highlight the importance of oral transmission in mediating the competition between horizontal (stercorarian) and vertical transmission; its presence as a competing contact process advantages vertical transmission even without adaptation to oral transmission, but such adaptation appears necessary to explain the persistence of (vertically-adapted) T. cruzi IV in raccoons and woodrats in the southeastern United States.

Keywords: Trypanosoma cruzi; horizontal transmission; vertical transmission; trade-off; cross-immunity

MSC 2010: 92D15; 92D30; 92D40

1. Introduction

Evolutionary epidemiology describes the adaptation of pathogens to selection pressure in host populations. The protozoan parasite Trypanosoma cruzi offers an opportunity to extend this field in two ways: by considering vector-transmitted disease, where host–vector cycles present a more complex landscape for pathogen evolution, and by considering interstrain competition as a selective force driving specialization towards distinct transmission modes. This pathogen, native to the Americas, is enzootic in host–vector cycles from the central USA to the southern cone, involving hundreds of mammalian host species and dozens of triatomine vector species. Although T. cruzi is best known as the etiological agent of Chagas’ disease, affecting millions of people throughout

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†Dedicated to the memory of our colleague Ioana Elise Hociota
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Latin America, it is the sylvatic cycles which maintain the parasite, with vectors infected in the wild continually moving to human habitations in search of new bloodmeal sources. In the USA, where Chagas’ disease is little-known, recent concerns in this regard have focused on the risk of transmission by transfusion or organ transplants from individuals (including immigrants) infected in Latin America. As a result, the sylvatic cycles in the USA have been less studied despite the often high (over 50%) prevalence of infection observed in some sylvatic US hosts. Only recently have studies begun to examine the characteristics particular to the sylvatic infection cycles that keep *T. cruzi* in zoonosis in the USA (some recent relevant summaries include [12,19,23,41]).

In the southeastern United States (SE US), in a region extending from eastern Texas to the Atlantic coast, the primary *T. cruzi* hosts are raccoons (*Procyon lotor*) and Virginia opossums (*Didelphis virginiana*). The main vector species associated with these hosts is *Triatoma sanguisuga* (other members of the *Triatoma lecithicularia* complex which includes *T. sanguisuga* have also been observed). To the west of this region, in parts of Texas and northern Mexico dominated by desert scrub, *Triatoma gerstaeckeri* is the dominant species, associated in sylvatic settings almost exclusively with the southern plains woodrat (*Neotoma micropus*). Strains of *T. cruzi* have been classified by phylogenetic lineage as belonging to one of six types, I–VI (formerly I and IIa–e); while all six types cocirculate in South America, only types I and IV (formerly IIa) have been identified in the USA [39]. Type I, which is associated with Chagas’ disease and human infections, is the only type found in Virginia opossums, as they have been found immune to type IV [41], consistent with the association of South American opossums with type I infections there [50]. Other sylvatic US hosts, including raccoons (as well as skunks, foxes, and armadillos), are associated instead with *T. cruzi* IV [17,39]. Most recently, both strains have been found in Texas woodrats [5].

The traditional means of infection with *T. cruzi* involves the vector feeding on a host. Vectors become infected via a bloodmeal on an infected host, following which the parasite reproduces in the vector’s gut. Hosts become infected when the parasite comes into contact with their mucous membranes or with a lesion in the skin; typically the vector defecates near the feeding site shortly after feeding, and the host scratches the bite area, inadvertently rubbing the parasite into the wound. This is referred to as stercorarian transmission. Vertical (congenital) transmission, which has been observed in humans as well as laboratory rats [28,43], may also be significant among other placental hosts (but not in marsupials such as opossums). Furthermore, it has been suggested that oral transmission of *T. cruzi* via host consumption of infected vectors (raccoons and opossums are both opportunistic feeders whose diets include insects) may be the dominant infection pathway in some cycles, more likely among raccoons than among opossums [32,37,40,49]. Oral transmission has also been documented in laboratory mice as well as in humans [4,7] and other primates [35]. Oral transmission is a risky adaptation in evolutionary terms since the consumed vector can infect at most one host this way, as opposed to potentially many via stercorarian transmission, but as shown in [24] it can, under some conditions, maintain sylvatic cycles alone. Indeed, it may not be any riskier than stercorarian transmission, which by its nature is less efficient than the more classical vector-borne transmission seen in mosquito-transmitted diseases, where vector feeding transmits the parasite directly into the host from the vector’s salivary glands.

In the SE US, the vectors *T. sanguisuga* and *T. gerstaeckeri* have long been observed to be inefficient vectors [33] because of their cautious feeding behaviour – they avoid climbing completely onto the host – and the long mean time between feeding and defecation. As a result, other avenues of transmission may be more important to maintaining the sylvatic cycles found in the SE US. In particular, the vectors’ inefficiency at stercorarian transmission may make oral and vertical transmission successful competition strategies when *T. cruzi* is under strong selection pressure to increase its host infection rate, either by improving its stercorarian transmission rate or by adapting to other transmission modes. Each of these modes involves a different mechanism for which pathogen strains may be more or less adapted. Each transmission cycle (host–vector
association) has unique characteristics (vector–host density ratio, host predation rate on vectors, etc.) which can shape adaptation by advantaging one transmission mode over others.

Infection with a given strain of *T. cruzi* has been observed \([26,31]\) to confer immunity against infection by other strains. This cross-immunity highlights a competition between strains for access to hosts and vectors, and one hypothesis is that this competition has driven adaptations in the strains to specific modes of transmission in order to persist. In particular, *T. cruzi* IV is often described as being less virulent than type I \([30,38,44]\), but appears to be better adapted to vertical transmission (by a factor of 2 in one study \([17]\)), and may also be better adapted to oral transmission, to both of which raccoons – the target host for type IV in the SE US since opossums are immune to it – are more vulnerable than opossums, as noted above. (Neither of these modes has yet been studied in woodrats.) Theory developed for directly transmitted pathogens suggests that a trade-off occurs between vertical and horizontal (classical) transmissibility \([27,42]\). This trade-off postulates a correlation between virulence and transmission, holding that more virulent – and hence more transmissible by classical means – strains should be favoured when hosts are numerous, and less virulent strains – which, being less harmful to hosts, may make vertical transmission more successful – when hosts are scarce \([46]\). Such theory is not well-established for vector-transmitted diseases, where new factors come into play. For example, the relative efficiency of different transmission modes may depend on the vector–host density ratio (when it is low, hosts are plentiful relative to vectors, so may not be bitten as often – does this scenario then favour alternative transmission modes?). In addition, in the case of *T. cruzi* in the SE US, pathogen-related mortality is not customarily observed in the primary hosts, so any notion of virulence associated with horizontal (here, stercorarian) transmission to hosts must be clarified. The present study focuses on the trade-off between stercorarian transmission and vertical (and perhaps oral) transmission hypothesized to occur in *T. cruzi* strains competing in sylvatic cycles in the SE US.

Although evidence of such evolutionary adaptations remains circumstantial and indirect at present, the competition between strains can be studied theoretically using mathematical models. Most theoretical studies of *T. cruzi* transmission have heretofore been limited to domestic transmission involving humans, including by transfusion \([36,48]\), but modelling has been used to study many other vector-borne diseases, including vertical transmission in dengue vectors \([14]\). Variable adaptation to vertical transmission has been studied in infections transmitted purely horizontally \([1,9,15]\), including Dhirasakdanon and Thieme’s \([9]\) finding of persistence in vertically transmitted parasite strains that provide cross-immunity against infection by more virulent strains transmitted purely horizontally, a situation not unlike the competition hypothesized between *T. cruzi* I and IV here. The contact process(es) that drive the transmission of pathogens between two distinct populations, however, saturate in one or the other population, as a function of the ratio of the two densities. Recently, Kribs–Zaleta \([21,23,24]\) developed models for sylvatic *T. cruzi* transmission which incorporate stercorarian, oral and vertical transmission to hosts, finding that for cycles involving raccoons and opossums the feeding processes of both hosts and vectors are likely saturated in vectors, and hence primarily dependent on host population density, and also that oral transmission is likely the dominant means of infection for raccoons in the SE US, even if raccoon predation on vectors is rare, thanks in part to a boost by vertical transmission. For woodrats, meanwhile, estimates \([23]\) suggest that the two processes are saturated in different densities, leading to potentially different selection pressures and different interstrain competition outcomes.

The present study builds on this work by extending the models to examine the competition between *T. cruzi* I and IV in cycles involving a placental host such as raccoons or woodrats, and the vector *T. sanguisuga* or *T. gerstaeckeri* (respectively), in order to describe the role played by possible evolutionary adaptations in determining the outcome of this competition. The next section develops a model to describe the underlying dynamics and establishes a framework for evaluating adaptation’s influence on the competition, through a trade-off between transmission...
modes. Analysis of the resulting dynamics focuses on reproductive numbers for the infection, which permit evaluation of the role of adaptive trade-offs between transmission modes on the interstrain competition. We consider raccoon-\textit{T. sanguisuga} and woodrat-\textit{T. gerstaeckeri} cycles separately since disparities in the vector–host ratio, host (predator) functional response, and other characteristics may shape adaptation differently.

2. Model formulation

2.1. Underlying dynamics

To describe the competition between \textit{T. cruzi} I and IV, we extend the host–vector infection model of [24] to a two-strain model, summarizing first the underlying assumptions. For simplicity in modelling vertical transmission, we consider only female hosts, and assume that a proportion \(p_j\) (\(j = 1, 2\)) of hosts infected with strain \(i\) give birth to infected young. There is no vertical transmission in vectors since parasites reside only in the gut of infected vectors. Rates for both types of feeding contacts – vector bloodmeals, which lead to vector infections of type \(j\) (\(j = 1, 2\)) at rate \(c_{vj}\) and to stercorarian infection of hosts with strain \(j\) at rate \(c_{hj}\) (both in units of \(1/\text{time}\)), and host predation (effort, in units of vectors/host/time) \(E_h\) on vectors – are assumed to depend on the vector–host population density ratio \(Q = N_v/N_h\) [2]. A proportion \(\rho_j\) of hosts that consume a vector infected with strain \(j\) become infected with that strain. We also assume simple demographics for both host and vector, e.g. logistic reproduction and linear \textit{per capita} mortality.

Since sharp saturation in contact rates (such as piecewise linear, corresponding to Holling type I) has been shown to exhibit a wider variety of behaviours than smooth saturation (such as Holling type II) [20–22], we initially consider the three contact rates mentioned above to follow such (piecewise linear) sharp saturation, defining:

\[
\begin{align*}
    c_{hj}(Q) &= \beta_{hj} \min \left( \frac{Q}{Q_v}, 1 \right), \\
    c_{vj}(Q) &= \beta_{vj} \min \left( \frac{1/Q_v}{1/Q_v}, 1 \right) = \beta_{vj} \min \left( \frac{Q_v}{Q}, 1 \right), \\
    E_h(Q) &= H \min \left( \frac{Q}{Q_h}, 1 \right),
\end{align*}
\]

as in Equation (2) of [24], with maximum values \(\beta_{hj}, \beta_{vj} (j = 1, 2)\) and \(H\), respectively, and respective saturation thresholds \(Q_v\) (for vector feeding) and \(Q_h\) (for host predation). Thus, the

| Var.       | Meaning                              | Units             |
|------------|--------------------------------------|-------------------|
| \(S_h(t)\) | Density of uninfected hosts          | hosts/area        |
| \(I_{h1}(t)\) | Density of hosts infected with \textit{T. cruzi} I | hosts/area        |
| \(I_{h2}(t)\) | Density of hosts infected with \textit{T. cruzi} IV | hosts/area        |
| \(S_v(t)\) | Density of uninfected vectors        | vectors/area      |
| \(I_{v1}(t)\) | Density of vectors infected with \textit{T. cruzi} I | vectors/area      |
| \(I_{v2}(t)\) | Density of vectors infected with \textit{T. cruzi} IV | vectors/area      |
| \(Q\)     | Vector–host population density ratio \((N_v/N_h)\) | vectors/host      |
| \(c_{hj}(Q, Q_v)\) | Strain \(j\) stercorarian infection rate | 1/time            |
| \(c_{vj}(Q, Q_v)\) | Strain \(j\) vector infection rate  | 1/time            |
| \(E_h(Q, Q_h)\) | Per-host predation rate              | vectors/host/time |
host-related rates $c_{hv}$ and $E_h$ saturate for high vector–host ratios, while the vector-related infection rate $c_{vj}$ saturates for low vector–host ratios.

Variables, notation, and parameters are summarized in Tables 1 and 2, with baseline parameter estimates either taken from [23] or developed in Appendix 1. Here the total vector density is $N_v = S_v + I_{v1} + I_{v2}$, and similarly for $N_h$, while the total vector birth rate is given by the function $b_v$, say $b_v(N) = r_v N (1 - N/K_v)$, and analogously for the host birth rate $b_h$. The resulting dynamics can be summarized by the flowchart in Figure 1 and by the following system of ordinary differential equations:

\[
S_h'(t) = \left( 1 - \frac{p_1 I_{h1}(t) - p_2 I_{h2}(t)}{N_h} \right) b_h(N_h) - \frac{[c_{h1}(Q(t)) + \rho_1 E_h(Q(t))] S_h(t)}{N_v(t)} I_{v1}(t) + [c_{h2}(Q(t)) + \rho_2 E_h(Q(t))] S_h(t) \frac{I_{v2}(t)}{N_v(t)} - \mu_h S_h(t),
\]

\[
I_{h1}'(t) = p_1 \frac{I_{h1}(t)}{N_h} b_h(N_h) + [c_{h1}(Q(t)) + \rho_1 E_h(Q(t))] S_h(t) \frac{I_{v1}(t)}{N_v(t)} - \mu_h I_{h1}(t),
\]

\[
I_{h2}'(t) = p_2 \frac{I_{h2}(t)}{N_h} b_h(N_h) + [c_{h2}(Q(t)) + \rho_2 E_h(Q(t))] S_h(t) \frac{I_{v2}(t)}{N_v(t)} - \mu_h I_{h2}(t),
\]

\[
S_v'(t) = b_v(N_v(t)) - c_{v1}(Q(t)) S_v(t) \frac{I_{h1}(t)}{N_h} - c_{v2}(Q(t)) S_v(t) \frac{I_{h2}(t)}{N_h} - \mu_S S_v(t)
\]

\[
- E_h(Q(t)) N_h \frac{S_v(t)}{N_v(t)},
\]

\[
I_{v1}'(t) = c_{v1}(Q(t)) S_v(t) \frac{I_{h1}(t)}{N_h} - \mu_S I_{v1}(t) - E_h(Q(t)) N_h \frac{I_{v1}(t)}{N_v(t)},
\]

\[
I_{v2}'(t) = c_{v2}(Q(t)) S_v(t) \frac{I_{h2}(t)}{N_h} - \mu_S I_{v2}(t) - E_h(Q(t)) N_h \frac{I_{v2}(t)}{N_v(t)}.
\]

The estimates derived in [23] imply that in practice $Q \approx \frac{128}{0.08} = 1600 > Q_h, Q_v$ for the raccoon-\textit{T. sanguisuga} transmission cycle, so that both types of host–vector contact processes are saturated.
The trade-off between adaptations to distinct transmission modes manifests in the dynamical nature of relevant evolutionary trade-offs can now be described as relationships among a given strain representing adaptation away from it (i.e. a complete inability to transmit via that mode). Then for a value of 1 representing full adaptation towards the given transmission mode and a value of 0 the respective degrees of specialization towards stercorarian, vertical, or oral transmission, with

\[
C_j = [c_{hj}(Q) + \rho_j E_h(Q)]I_{hj}/N_h \quad (j = 1, 2)
\]

is used.

Figure 1. Flow chart illustrating model (2). All rates given are per capita except birth rates. For space constraints, the notation \( C_j = [c_{hj}(Q) + \rho_j E_h(Q)]I_{hj}/N_h \quad (j = 1, 2) \) is used.

in vectors and thus driven by host density, while \( Q_h < Q < Q_v \) for the woodrat- \( T. gerstaeckeri \) transmission cycle \( Q = \frac{128}{9.33} \approx 14 \). We therefore take the corresponding terms from Equation (1), making

\[
c_{hj} = \beta_{hj}, \quad c_{vj} = \frac{\beta_{vj} Q_v}{Q} \quad (i = 1, 2), \quad \text{and} \quad E_h = H
\]

for the raccoon- \( T. sanguisuga \) transmission cycle, while

\[
c_{hj} = \frac{\beta_{hj} Q}{Q_v}, \quad c_{vj} = \beta_{vj} \quad (i = 1, 2), \quad \text{and} \quad E_h = H
\]

for the woodrat- \( T. gerstaeckeri \) transmission cycle. We consider these two cycles separately in the numerical work that follows, in order to see how the changes in saturation status affect \( T. cruzi \) interstrain competition for hosts.

2.2. Adaptive trade-off

The trade-off between adaptations to distinct transmission modes manifests in the dynamical model of Section 2.1 through the host infection parameters \( \beta_{hj} \) (stercorarian), \( p_j \) (vertical) and \( \rho_j \) (oral) for each strain. In order to explore the effects of this trade-off, we rewrite these parameters to make the degree of specialization explicit. In particular, we define variables \( x, y, \) and \( z \) to be the respective degrees of specialization towards stercorarian, vertical, or oral transmission, with a value of 1 representing full adaptation towards the given transmission mode and a value of 0 representing adaptation away from it (i.e. a complete inability to transmit via that mode). Then for a given strain \( j \), we can write \( \beta_{hj} = \beta_{hmax}x_j, \quad p_j = p_{max}y_j \), and \( \rho_j = \rho_{max}z_j \), with \( x_j, y_j, z_j \in [0, 1] \).

The nature of relevant evolutionary trade-offs can now be described as relationships among \( x, y, \) and \( z \).

In this study, we assume that a trade-off exists between stercorarian and vertical transmission, so that \( x = 1 \) implies \( y = 0 \), and \( y = 1 \) implies \( x = 0 \). The trade-off is described by the relation \( y = g(x) \), where \( g(x) : [0, 1] \rightarrow [0, 1] \) defines the nature of the trade-off. Trade-off is typically described qualitatively as strong, neutral, or weak, depending on the relative gains and losses at each degree of specialization (see Figure 2). Strong trade-offs mean that specialists (\( x = 0 \) or \( x = 1 \)) lose more in their specialty than they gain in the other type of transmissibility as they move away from the extremes, creating a curve that is concave down. Under weak trade-offs, specialists gain more in the other type of specialty than they lose in their own as they move away from either extreme, creating a curve that is concave up. In a neutral trade-off, gains or losses in either specialty are exactly offset by corresponding losses or gains in the other specialty. To describe these trade-offs mathematically, we use the symmetric curve \( g(x) = (1 - x^{1/\alpha})^\alpha \) [25],
Figure 2. Weak, neutral, and strong trade-offs between two specialties as described by the symmetric function $y = g(x) = (1 - x^{1/\alpha})^\alpha$, with $\alpha = \frac{1}{2}$, 1, and 2, respectively.

where $\alpha$ is a dimensionless parameter measuring the strength of the trade-off. In this study, we shall use $\alpha$ values of $\frac{1}{2}$, 1, and 2 to describe weak, neutral, and strong trade-offs, respectively.

Since there is not yet any data on whether oral transmissibility is aligned with vertical transmissibility, we shall consider both the case in which oral transmissibility is independent of the stercorarian-vertical adaptation (i.e. $z_j$ is fixed), and the case in which oral transmissibility is aligned with vertical transmissibility (i.e. $z_j = y_j$). Finally, in studying trade-off, we assume that with just a single mode of vector infection, and parasites in a different life stage within vectors than within hosts, vector infection rates are unaffected by the trade-off, i.e. $\beta_{v1} = \beta_{v2} = \beta_v$.

Adaptation along the trade-off curve $y = g(x)$ is typically tracked using $x$ as an index variable, with the spectrum of possible strains varying from $x = 0$ to $x = 1$. However (as observed in [25]), for extreme values of the trade-off strength $\alpha$ ($\alpha \to 0$ or $\alpha \to \infty$) half of the curve (beginning at the midpoint, where $x = y$) becomes nearly vertical, making it difficult if not (in the limiting cases) impossible to distinguish among these adaptive outcomes using $x$ as an index variable, since their $x$-coordinates are compressed toward either 0 or 1. That is, for extremely weak trade-offs ($\alpha \to 0$), half of the spectrum for which $x > y$ is compressed toward $x = 1$; meanwhile, for extremely strong trade-offs ($\alpha \to \infty$) half of the spectrum for which $x < y$ is compressed toward $x = 0$. In either case $x$ becomes unsuitable as an index variable. It may, therefore, be more helpful to use instead the variable $\Delta = x - y$ as an index of a strain’s location along the trade-off curve; as $x$ goes from 0 to 1 (and $y$ from 1 to 0), $\Delta$ goes from $-1$ to 1, with the midpoint at 0. This avoids the compression issues at the endpoints. We then evaluate the competition on the subset $[-1, 1] \times [-1, 1]$ of the $(\Delta_1, \Delta_2)$ plane. Figure 3 illustrates how any pair of points on the curve $y = g(x)$ corresponds to a unique point in the $(\Delta_1, \Delta_2)$ plane as well as a unique point in the $(x_1, x_2)$ plane. This framework shift from $x$ to $\Delta$ maintains the notion of the arclength as the genetic distance and hence the primary measure of adaptation. By assumption strain 1 ($T. cruzi$ I) will be taken as further adapted toward stercorarian transmission than strain 2 ($T. cruzi$ IIa/IV), so that $x_1 > x_2$, and $\Delta_1 > \Delta_2$.

From adaptive dynamics [10], a pairwise invasibility plot is a useful graphical representation of competition between two variants of an organism, in which the outcome is given for each ordered pair of the two variants’ values of the characteristic which distinguishes them. These plots will be used in the next section after analysis of the infection dynamics provides a fitness measure by which to determine a competition’s outcome.
3. Analysis

3.1. Model dynamics

The behaviour of model (2) can be described by studying first the overall host and vector density dynamics, and then simplifying the model to focus on the infection dynamics, where reproductive numbers determine the outcome of the interstrain competition. If we write equations for the total host and vector densities, summing the respective trios of equations in (2), we find that

\[ N_h'(t) = b_h(N_h(t)) - \mu_h N_h(t), \]
\[ N_v'(t) = b_v(N_v(t)) - \mu_v N_v(t) - E_h(Q(t))N_h(t). \]  

For most forms of birth rate function \( b_h(N_h) \), including constant and logistic, Equation (5) has a single globally stable equilibrium \( N_h^* \) (for instance, if \( b_h(N) = r_hN(1 - N/K_h) \), then \( N_h^* = K_h(1 - \mu_h/r_h) \)); thus \( N_h(t) \to N_h^* \) as \( t \to \infty \) regardless of initial condition. This leads us to consider Equation (6) for \( N_v \) with \( N_h = N_h^* \). As in the simpler models studied in [21,24], the vector density dynamics thus decouple from the infection dynamics, and can be studied separately. As detailed in [21,22], the dynamics of \( N_v(t) \) depend on two dimensionless quantities, rescaled versions of the maximum predation rate \( HN_h^* \) and the saturation threshold \( Q_hN_h^* \), and may exhibit one of four behaviours: (i) the vectors go extinct; (ii) the vectors persist at a unique equilibrium level; (iii) an Allee effect occurs, with extinction and persistence both possibilities depending on initial density; and (iv) the vectors persist at one of two different survival equilibrium densities (each of which then generates a different value for the basic \( T. cruzi \) reproductive number \( R_0 \)).

This last behaviour (positive bistability) occurs for all predator functional responses \( E_h \) which saturate more sharply than Holling type II saturation [22]; all other behaviours also occur even for smooth saturation in \( E_h \). Vector extinction requires \( H > (r_v - \mu_v)Q_h \).

In practice, however, high predation on vectors by any \( T. cruzi \) host has not been documented, let alone vector extinction as a result. We will, therefore, assume henceforth that vector population dynamics have reached a stable equilibrium level \( N_v^* > 0 \), and by a theorem of Thieme [45] pass to the limiting system of (2) in which \( N_h(t) = N_h^* \), \( N_v(t) = N_v^* \). We can thus eliminate \( S_h \) by defining it as \( N_h^* - I_h1 - I_h2 \), and similarly for \( S_v \). (To simplify notation, we henceforth write \( N_h, N_v \).)
The overall context, therefore, produced into a population in which the other strain is already endemic \[8,34,51\]. In a cross-immunity number of secondary infections of the given strain produced by a single infected individual introduced into a completely naive population. The resulting model can thus be further simplified by introducing the following notation: \(\tilde{\beta}_{ij} = c_{ij}(Q^*), \tilde{\beta}_{ij} = c_{ij}(Q^*)\) \((j = 1, 2)\), \(\tilde{\mu}_v = \mu + E_h(Q^*)/Q^*\) (all with units time). The infection dynamics can thus be studied via the system

\[
\begin{align*}
I_{1h} &= \frac{\tilde{\beta}_{h1}S_h(t)I_{1v}(t)}{N_v} + p_1\mu_hI_{1h}(t) - \mu_hI_{1h}(t), \\
I_{2h} &= \frac{\tilde{\beta}_{h2}S_h(t)I_{2v}(t)}{N_v} + p_2\mu_hI_{2h}(t) - \mu_hI_{2h}(t), \\
I_{1v} &= \frac{\tilde{\beta}_{v1}S_v(t)I_{1h}(t)}{N_h} - \tilde{\mu}_vI_{1v}(t), \\
I_{2v} &= \frac{\tilde{\beta}_{v2}S_v(t)I_{2h}(t)}{N_h} - \tilde{\mu}_vI_{2v}(t),
\end{align*}
\]

which can be shown to exhibit competitive exclusion, similar to other previously studied models for competing pathogen strains with cross-immunity \[3,16\]. Examination of the steady-state conditions shows system \((7)\) to have three equilibria: the disease-free equilibrium \(E_0(0, 0, 0, 0)\), the equilibrium in which only strain 1 is endemic \(E_1(i_{h1}^*, N_h, 0, i_{v1}^*, N_v, 0)\), and the equilibrium in which only strain 2 is endemic, \(E_2(0, i_{h2}^*, N_h, 0, i_{v2}^*, N_v)\), where the equilibrium prevalence levels are given by

\[
i_{hj}^* = \frac{\tilde{\beta}_{hj}\tilde{\beta}_{vj} - (1 - p_j)\mu_h\tilde{\mu}_v}{\tilde{\beta}_{ij}(\tilde{\beta}_{hj} + (1 - p_j)\mu_h)}, \quad i_{vj}^* = \frac{\tilde{\beta}_{hj}\tilde{\beta}_{vj} - (1 - p_j)\mu_h\tilde{\mu}_v}{\tilde{\beta}_{hj}(\tilde{\beta}_{vj} + \tilde{\mu}_v)}.
\]

(No coexistence endemic equilibrium exists except in the trivial case where all parameters are equal.)

In order to describe existence and stability conditions for these equilibria, we must define the basic reproductive numbers \(R_1\) and \(R_2\) for strains 1 and 2, respectively, and the invasion reproductive numbers (IRNs) \(\tilde{R}_1\) and \(\tilde{R}_2\) for the respective strains. The basic reproductive number for a given strain, a familiar and key quantity in mathematical epidemiology, gives the mean number of secondary infections produced by a single infected individual (host or vector) introduced into a completely naive population. The invasion reproductive number (IRN) gives instead the mean number of secondary infections of the given strain produced by a single infected individual introduced into a population in which the other strain is already endemic \[8,34,51\]. In a cross-immunity context, therefore, \(\tilde{R}_j < R_j\). Both reproductive numbers can be calculated using next-generation operator approaches \[11,47\] (for the IRN, only the invading strain is considered to be an infection, and the endemic equilibrium for the resident strain is used in place of the disease-free equilibrium); the results are as follows:

\[
R_1 = \frac{1}{2} \left( p_1 + \sqrt{p_1^2 + 4(1 - p_2)\tilde{\beta}_{h1}\tilde{\beta}_{v1}/\mu_h\tilde{\mu}_v} \right), \quad R_2 = \frac{1}{2} \left( p_2 + \sqrt{p_2^2 + 4(1 - p_1)\tilde{\beta}_{h2}\tilde{\beta}_{v2}/\mu_h\tilde{\mu}_v} \right),
\]

\[
\tilde{R}_1 = \frac{1}{2} \left( p_1 + \sqrt{p_1^2 + 4(1 - p_2)\tilde{\beta}_{h1}\tilde{\beta}_{v1}/\mu_h\tilde{\mu}_v} \right), \quad \tilde{R}_2 = \frac{1}{2} \left( p_2 + \sqrt{p_2^2 + 4(1 - p_1)\tilde{\beta}_{h2}\tilde{\beta}_{v2}/\mu_h\tilde{\mu}_v} \right).
\]

The overall \(T. cruzi\) basic reproductive number is \(R_0 = \max(R_1, R_2)\); some strain of \(T. cruzi\) remains enzootic in the given host–vector transmission cycle if \(R_0 > 1\). If only one of \(R_1\) and \(R_2\)
is greater than 1, then the corresponding strain is the one which remains endemic. If both exceed 1, then in theory coexistence could occur if in addition $R_1 > 1$ and $R_2 > 1$. However, some algebra shows that

$$\tilde{R}_1 > 1 \iff \frac{\tilde{\beta}_{h1}\tilde{\beta}_{v1}}{(1-p_1)} > \frac{\tilde{\beta}_{h2}\tilde{\beta}_{v2}}{(1-p_2)} \iff \tilde{R}_2 < 1,$$

(8)

so it is impossible for both IRNs to exceed 1 simultaneously, which implies competitive exclusion. We can also observe that in these expressions, the vertical transmission terms are separate from the horizontal (other) transmission terms, the latter of which are grouped together as

$$R^2_{hj} = \tilde{\beta}_{hj}\tilde{\beta}_{vj}/\mu h\tilde{\mu}_v \ (j = 1, 2).$$

The proofs defining these reproductive numbers in terms of next-generation operators establish local asymptotic stability of the three equilibria: $E_0$ alone if $R_0 \leq 1$, $E_1$ alone if $R_0 > 1$ and $\tilde{R}_1 > 1$, and $E_2$ alone if $R_0 > 1$ and $\tilde{R}_2 > 1$ (thus partitioning the entire parameter space into three regions)\(^2\). This local stability can be extended to global stability in some cases, as illustrated by the following result, the proof of which (given in Appendix 2) uses a standard application of Lyapunov functions.

If $R_0 \leq 1$, the disease-free state $E_0$ of system (7) is globally asymptotically stable (GAS).

The strain 1 endemic state $E_1$ is GAS under any of the following three sets of conditions:

(i) $R_2 \leq 1$ and $1 \leq \frac{\tilde{\beta}_{h2}}{\mu_{h1}} \leq 1 + \frac{\tilde{\beta}_{v2}}{\tilde{\mu}_v}$;

(ii) $p_1 = p_2$, $\tilde{\beta}_{h1} < \tilde{\beta}_{h2}$, and $\frac{f_1(\tilde{\beta}_{h2})}{f_1(\tilde{\beta}_{h1})} \leq 1 + \frac{1}{R_2} - \frac{1}{R_1}$; or

(iii) $p_1 = p_2$, $\tilde{\beta}_{h1} > \tilde{\beta}_{h2}$, and $\left(\frac{1 - f_1(\tilde{\beta}_{h2})}{1 - f_1(\tilde{\beta}_{h1})}\right)R_2 \leq R_1$,

where $\tilde{\mu}_{hj} = (1-p_j)\mu_{hj}, R_{hj} = \tilde{\beta}_{hj}\tilde{\beta}_{vj}/\mu_{hj}\tilde{\mu}_v$, and $f_j(x) = x/(x + \tilde{\mu}_{hj}) \ (j = 1, 2)$. Likewise, the strain 2 endemic state $E_2$ is GAS under any of the following three sets of conditions:

(i) $R_1 \leq 1$ and $1 \leq \frac{\tilde{\beta}_{h1}}{\mu_{h2}} \leq 1 + \frac{\tilde{\beta}_{v1}}{\tilde{\mu}_v}$;

(ii) $p_1 = p_2$, $\tilde{\beta}_{h1} < \tilde{\beta}_{h2}$, and $\left(\frac{1 - f_2(\tilde{\beta}_{h1})}{1 - f_2(\tilde{\beta}_{h2})}\right) \frac{R_{1+}}{R_{2+}} \leq \frac{R_{2+}}{R_{1+}}$; or

(iii) $p_1 = p_2$, $\tilde{\beta}_{h1} > \tilde{\beta}_{h2}$, and $\frac{f_2(\tilde{\beta}_{h2})}{f_2(\tilde{\beta}_{h1})} \leq 1 + \frac{1}{R_1} - \frac{1}{R_2}$.

A note regarding the quantities $R_{j+}$ defined above: it is straightforward to prove that $R_{j+} > 1 \iff R_j > 1$, and $R_{j+} > \max(1, R_{k+}) \ (k \neq j) \iff \tilde{R}_j > 1$. The first of these facts implies that $\tilde{R}_j < R_j \iff R_k > 1 \ (k \neq j)$, reflecting the increased difficulty of invasion when another strain is present. In these terms, we can also write $i_{hj}^* = (1 - 1/R_{j+})f_j(\tilde{\beta}_{hj})$.

### 3.2. Trade-off and competition

The deterministic model (2) can, therefore, be used to predict the outcome of interstrain $T. cruzi$ competition by identifying which (if either) of the two strains’ IRNs exceeds 1. As observed in Equation (8), the question of which strain’s IRN exceeds 1 is mathematically equivalent to which strain $[j]$ has the greater value of the expression $\tilde{\beta}_{hj}\tilde{\beta}_{vj}/(1 - p_j)$. We can rewrite this expression as a function of the degrees of adaptation to stercorarian transmission $x$ and vertical transmission.
y: without adaptation to/from oral transmission, it is $\mathcal{H}(x, y) = k(x + a)/(1 - by)$, where

$$k = \beta_{h_{\text{max}}} \min \left( \frac{Q}{Q_v}, 1 \right) \beta_v \min \left( \frac{Q_v}{Q}, 1 \right) = \beta_{h_{\text{max}}} \beta_v \min \left( \frac{Q}{Q_v}, \frac{Q_v}{Q} \right),$$

$$a = \rho_{\text{max}} H \min (Q/Q_h, 1)/\beta_{h_{\text{max}}} \min (Q/Q_v, 1)$$

is the relative importance of oral transmission over stercorarian at their maxima, and $b = \rho_{\text{max}}$. Similarly, with adaptation to oral transmission aligned with that to vertical, $\mathcal{H}(x, y) = k(x + ay)/(1 - by)$. In both cases, $\mathcal{H}$ is an increasing function of both $x$ and $y$ on the unit square. As noted in Section 2.2, since $x$ and $y$ are assumed constrained by the trade-off relation $y = g(x)$, this fitness measure can be written as a function $h$ of a single variable $\Delta = x - y$ representing the location along the trade-off curve. Whichever strain has a higher value of $h(\Delta) = h(x - g(x)) = \mathcal{H}(x, g(x))$ then wins the competition. Note that the forward diagonal $\Delta_1 = \Delta_2$ automatically serves as one boundary where both strains have the same value of $h$.

Since the $h$-values of the two endpoints of the spectrum are independent of the trade-off strength $\alpha$, we consider separately the two cases $h(-1) < h(1)$ and $h(-1) > h(1)$. We first note that $h(-1) = \mathcal{H}(0, 1) = ka/(1 - b)$; then, without adaptation to/from oral transmission (AOT), $h(1) = k(a + 1)$, while with AOT, $h(1) = k$. Thus the case $h(-1) < h(1)$ simplifies to $(a + 1)b < 1$ without AOT and $a + b < 1$ with AOT.

The pairwise invasibility plots in Figure 4 depict outcomes of the competition (a) without, and (b) with, AOT in the $(\Delta_1, \Delta_2)$ plane. For a neutral trade-off ($\alpha = 1$) the competition is independent of the magnitude of the difference in $\Delta$ and is instead entirely determined by the relative fitness of the two extremes – whichever strain is closer to the ‘fitter’ extreme wins. However, as the trade-off becomes stronger or weaker, the other strain gains an increasing area (in the triangle $\Delta_1 > \Delta_2$) in which it wins, until for extreme values of $\alpha$ ($\alpha \to 0$ and $\alpha \to \infty$), the areas are almost equal. Classical trade-off studies suggest that weak trade-offs favour generalists (i.e. $h$ has a maximum in the interior of $[-1, 1]$), so for $\Delta_1 > \Delta_2$ whichever strain is more like the optimal generalist (as measured by $h$) than the other is, wins. Strong trade-offs, meanwhile, favour specialists (i.e. $h$’s maximum is at one of the endpoints), so the winning strain must be less like (in terms of $h$) the generalist which minimizes $h$ than the other is; this can occur by being closer to the winning specialist, but it can also occur by being closer to the losing specialist (a local maximum of $h$) than the other strain is to the winning specialist.

We note that a comparison using $x$ instead of $\Delta$ would compress $3/4$ of the diagrams representing extreme values of $\alpha$ down into lines with no area; for $\alpha \to 0$ only the lower left quarter of the diagram would remain, and for $\alpha \to \infty$ only the upper right quarter of the diagram would remain. In both cases (cf. the eight relevant diagrams in Figure 4), the results would suggest that whichever strain has the greater $x$ value (i.e. is more adapted to stercorarian transmission) than the other would win, a result clearly at odds with the more symmetric picture provided using $\Delta$.

It can also be observed that the impact of AOT is quantitative rather than qualitative: if strain 2 is better adapted to both vertical and oral transmission than strain 1, then the region in parameter space in which it wins the competition is larger, but still generally the same shape.

Given the dearth of data from which to estimate several model parameters, one can also consider the effects of variation in parameters such as the maximum predation rate $H$ and the [equilibrium] vector–host ratio $Q$. Both of these parameters affect the competition through the quantity $a : H$ in a straightforward linear way, $Q$ in a more limited way. Since $a$ involves two saturation processes dependent on $Q$ with different saturation thresholds, as $Q$ rises the process with the lower threshold is advantaged. Estimates suggest here that $Q_{\text{ss}} < Q_s$, making $a$ an increasing function of $Q$ for $0 < Q < Q_s$, and independent of $Q$ when both processes are saturated ($Q > Q_s$). Thus increasing either parameter makes oral transmission more significant relative to stercorarian transmission, which advantages strain 2 even when both strains are equally orally transmissible.

The baseline parameter estimates developed in Appendix 1, which assume the general vector contact rate of raccoons and opossums to be the same (since they have similar size, eating, moving
and sleeping habits) and which assume 10% strain 2 vertical transmission \(p_{2r} = 0.1\), yield 
\[ \alpha = 0.862, x_1 = 0.755, x_2 = 0.431, \Delta_1 = 0.422, \Delta_2 = -0.236, \]
with \(a = 1.90\) and \(b = 0.15\) for the raccoon-\textit{T. sanguisuga} cycle, making \((a + 1)b = 0.435 < 1\) but \(a + b = 2.05 > 1\). Since \(\alpha\) is so close to 1 (i.e. the trade-off is relatively neutral), the competition is determined by the relative fitness of the two evolutionary extremes for most values of \(x\) or \(\Delta\), including those estimated above. With \((a + 1)b < 1\) but \(a + b > 1\), strain 2 only wins the competition if it is adapted to oral as well as vertical transmission, although (since here \(a + b > 2\)) the degree of adaptation need not be as strong as that to vertical transmission.
If we assume that vertical transmission is equally likely in woodrats and raccoons, with \( p_{2w} = 0.1 \), then for the woodrat-\textit{T. gerstaeckeri} cycle \( a = 0.533 \), making \((a + 1)b = 0.230 < 1\) and \(a + b = 0.689 < 1\), i.e. strain 1 should win regardless of AOT. The primary factor contributing to the difference from the raccoon cycle is not the difference in the vector–host ratio \( Q \) but the difference in lifespan \( 1/\mu_h \): a woodrat population is renewed (existing members die and new ones are born) 2.5 times as fast as raccoons, so in order to account for the observed prevalence, any infected woodrats ‘replaced’ by uninfected ones must be infected faster than raccoons. These results (for both cycles) hold for a relatively wide range of values of \( p \) (0–0.3) and \( \rho \) (0–0.4); higher values (roughly \( p \geq 0.5 \) and \( \rho \geq 0.6 \)) are inconsistent with observed prevalence since they would predict higher prevalence even without any stercorarian transmission whatsoever.

However, if we suppose that rats are more like the lab mice in [18] than like raccoons, strain 2 can win in the woodrat cycle as well. For the given values, if we assume that \( p_{2w} \geq 0.25 \) (hence \( p_w \max \geq 0.375 \) as in Table 2), then strain 2 wins if adapted to oral transmission, and for higher values of \( p_{2w} \) (e.g. 0.4) strain 2 wins even without AOT. The observation of both strains of \textit{T. cruzi} in woodrat populations can be understood in terms of this model by taking vertical transmission to occur at a higher proportion than in raccoons, at a level that places the two strains’ fitnesses at roughly equal levels, under which scenario local stochasticity can allow either to dominate.

4. Discussion

The dynamical system used in this study to describe sylvatic \textit{T. cruzi} transmission dynamics provides a framework for evaluating the competition between the two parasite strains native to the USA through fitness measures derived from the infection’s reproductive numbers. The fitness measure used here highlights the interplay among transmission avenues to the host – classical stercorarian transmission, vertical (congenital) transmission, and oral transmission via predation – in determining the outcome of this competition. Although adaptive trade-offs involving virulence and alternative transmission modes (in particular, horizontal versus vertical) are well-studied in the context of directly transmitted infections, this may be the first study of such a trade-off in the context of a vector-borne parasite, and the role of oral transmission as a third mode in mediating adaptation between the other two is especially significant. The outcome of this competition takes on special importance since the strain (\textit{T. cruzi} I) more adapted to stercorarian transmission is associated with Chagas’ disease in humans, and cross-immunity, which prevents co-infection, implies that if the other strain (\textit{T. cruzi} IV) can entrench itself in a sylvatic host population via improved vertical transmission, it may constitute a barrier against invasion by the Chagasic strain.

Estimates of infection-related rates and each strain’s degree of adaptation (based on comparison of type I infection rates in opossums and type IV infection rates in raccoons in the same region) suggest that for very modest vertical and oral transmission rates, strain IV must adapt to oral as well as vertical transmission in order to win the competition in raccoons (as observed). Under the same assumptions, strain I wins the competition in woodrats, but higher vertical or oral transmission rates (still lower than what has been observed in mice in laboratory conditions) allow strain IV to win. Field observations find both strains present in woodrat populations, which suggests that slightly higher vertical (or oral) transmission rates in woodrats place the competing strains on almost equal ground, where local stochastic effects and limited communication between neighbouring woodrat populations allow each parasite strain to make inroads.

Analysis also shows more generally how oral transmission as a second contact process saturating in the vector–host ratio (and sooner than stercorarian transmission does) acts as an important mediator in the competition (in favour of adaptation to vertical transmission), even when both strains are equally orally transmissible. That is, adaptation to oral transmission (aligned with that
to vertical transmission) is not as important to persistence of a primarily vertically transmitted strain as is the mere presence of oral transmission as a competing contact process with classical stercorarian transmission.

Further study of this competition using stochastic and/or multi-host models is warranted by reports of prevalence of *T. cruzi* I – at trace levels in raccoons [39] and more widespread among woodrats [5] – in transmission cycles where *T. cruzi* IV is established as enzootic. Although the deterministic model developed in this study predicts competitive exclusion, stochastic models can show how fluctuations in transient dynamics (which may last many years) can slow or even reverse its outcome on a local scale, allowing a strain to persist (and even displace another) when it would be normally expected to die out. Such research is already in progress.

Another significant factor in the geographical spread of *T. cruzi* is the interaction of multiple transmission cycles. First, vector species in any given area usually feed on multiple host species, notably raccoons and Virginia opossums in the SE US (as mentioned above) and raccoons and woodrats in parts of Texas, inevitably complicating the dynamics within each cycle. Second, both small-scale and large-scale spatial heterogeneities bring otherwise disjoint cycles into contact in ecological transition zones via the dispersal of vectors, which has been shown to be a key factor in domestic *T. cruzi* transmission [13] and is also likely to play an important role in communicating sylvatic cycles. Study of both these factors is already in progress (with some preliminary results, e.g. [6,29]); meanwhile, data about the underlying biology – such as infection rates from the various modes, and *T. cruzi* strain typing in woodrats and their vectors – is in the process of being collected.

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**Notes**

1. The vertical transmission terms are kept distinct from the host mortality terms in the first two equations for purposes of calculating reproductive numbers.
2. The bifurcation at $R_0 = 1$ is transcritical, as is typical in epidemiological models. The bifurcation at $\tilde{R}_1 = \tilde{R}_2 = 1$ is a degenerate transcritical bifurcation, as discussed in [6, Section 3.2].

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Appendix 1. Parameter estimation

Parameter estimates for the models in this paper (see Table 2) are taken from [23] except as detailed below. Note that Kribs-Zaleta [23] estimates $Q_v$ to be in the range $14 < Q_v < 800$, of which we take the approximate geometric mean 100, and $H$ to be in the range $0 < H < 100$, from which we here take $H = 1$.

All parameter estimates should be specific to the transmission cycle (host and vector species and location), but the extreme lack of data for the two cycles under study in this article leave no alternative but to extrapolate from the most closely related available data.

One very small ($n = 2$) study on oral transmission generated a 100% oral infection rate for raccoons fed vectors infected with $T. cruzi$ IV [40], so we shall take $P_{\text{max}} = 1$ as the maximum capacity of $T. cruzi$ to adapt to oral transmission. The only other two reports of observed oral transmission probability involved opossums and different parasite strains, and generated much lower estimates of 0.075 [37] and 0.15 [49]; the differences in host biology, vector species and parasite strain make it difficult to extend them to the two cycles under study here but may signal significant differences in oral transmissibility by strain and/or host. In the scenario in the main text which assumes no adaptation to/from oral transmissibility (AOT), we can take the weighted (by sample size) average of 0.177 from [23].

Estimates of the vertical transmission probability range between 1% and 10% in humans; one study of Wistar rats [28] (%)

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Estimates of the vertical transmission probability range between 1% and 10% in humans; one study of Wistar rats [28] found vertical transmission of about 9% for one parasite strain but none in another. Another study conducted with mice found vertical transmission of strain I at 33.3% (44/132) and of strain IIa/IV at 66.7% (104/156). Although $T. cruzi$ infection
is typically more acute in incidental hosts (such as lab mice) than in customary hosts like raccoons and woodrats, these results suggest that *T. cruzi* IV is twice as adapted to vertical transmission as is *T. cruzi* I (\(p_2 = 2p_1\), \(y_2 = 2y_1\), and take the figures above for \(y_1\) and \(y_2\), respectively (i.e. we assume \(p_{max} = 1\) for these lab mice; we estimate absolute \(p\) values for raccoons and woodrats below).

The only other parameter estimates not taken from [23] are the infection rates \(\beta\), which we back-calculate here based on observed prevalences, using the technique outlined in [23]. Table A1 provides estimates of *T. cruzi* infection prevalence in the various host and vector species, also taken from [23]. Note that studies reviewed in [23] which provided prevalence estimates did not identify parasite type or strain; although opossums are associated exclusively with *T. cruzi* I in the USA, while raccoons are associated with *T. cruzi* IIa, both strains have been found to be enzootic in woodrats, at roughly equal levels [5]. Vectors are presumably infected with the same strains as their respective hosts.

Using a simple one-strain SI host–vector model with constant population densities \(N_h\), \(N_v\),

\[
I_h' = \left[ c_h(Q) + \rho E_h(Q) \right] S_h(t) \frac{I_v(t)}{N_v} - (1 - p)\mu_h I_h(t),
\]

\[
I_v' = c_v(Q) S_v(t) \frac{I_h(t)}{N_h} - \mu_v I_v(t) - E_h(Q) \frac{N_h I_v(t)}{N_v},
\]

we can estimate infection rates as follows, using the equilibrium conditions:

\[
c_h(Q) + \rho E_h(Q) = \frac{(1 - p)\mu_h i_h^*}{i_h^*(1 - i_h^*)}, \quad c_v(Q) = \frac{(\mu_v + E_h(Q)/Q)i_v^*}{i_v^*(1 - i_v^*)},
\]

(A1)

where we assume that the average observed prevalences given in Table A1 reflect equilibrium prevalences \(i_h^*, i_v^*\). This is a reasonable assumption since *T. cruzi* is endemic in this region and has been for a long period of time. We disregard strain variation in the region and assume there is only one resident strain for a given cycle.

In estimating the vector–host ratio \(Q\) for the various cycles, we must take into account the fact that *T. sanguisuga* is associated with multiple hosts. We make the assumption that in the SE US the vectors are distributed evenly among raccoons (\(r\)) and opossums (\(o\)) in areas unpopulated by humans, making this ratio applied to raccoons

\[
Q_r = \frac{N_v}{N_v} \frac{N_r}{N_r + N_o} = \frac{N_v}{N_r + N_o},
\]

where \(N_r\) and \(N_o\) are the equilibrium population densities for raccoons and opossums, respectively. This yields an estimate of \(Q_r = \frac{128}{32} \approx 1060\). For woodrats we estimate \(Q_v = \frac{128}{7} \approx 14\). Since these estimates suggest that \(Q > Q_p\) for all cycles, we take \(E_h(Q) = H\). For cycles involving raccoons or opossums, given the estimate that \(Q > Q_p\), we take \(c_h(Q) = \beta_h\) and \(c_v(Q) = \beta_v Q_v/Q\). For cycles involving woodrats, where \(Q < Q_p\), we instead take \(c_h(Q) = \beta_h Q_v/Q\) and \(c_v(Q) = \beta_v\).

For purposes of estimating infection rates, we assume \(p_1 = 0.05\) and \(p_2 = 0.10\) for both raccoons and woodrats, in keeping with the usual 1–10% range. (Using a higher value of \(p\) such as the 0.667 value reported above actually generates a negative value of \(p_h\) – that is, vertical and oral transmission alone are then more than able to account for the observed prevalence, edging out stercorarian transmission altogether!) This implies that \(p_{max} = 0.15\) for these hosts. For purposes of estimating \(\beta_h\) and \(\beta_v\) we also apply Equations (A1) to an opossum-*T. sanguisuga* cycle, recalling that opossums (being marsupial) have no vertical transmission. Substituting these expressions and the estimated parameter and prevalence values from Tables 2 and A1, respectively, into Equations (A1) yields values for \(\beta_h\) and \(\beta_v\) for each cycle. The resulting estimates are given in Table A2.

Table A2. Estimates for infection rates in sylvatic *T. cruzi* transmission cycles (units 1/yr).

| Cycle                  | \(\beta_h\) | \(\beta_v\) |
|------------------------|-------------|-------------|
| Raccoon/T.s., SE US    | 0.225       | 9.67        |
| Opossum/T.s., SE US    | 0.394       | 13.4        |
| Woodrat/T.g., TX       | 5.77        | 1.59        |
Appendix 2. Global asymptotic stability proofs for system (7)

If $R_0 \leq 1$, then the disease-free state $E_0$ of system (7) is GAS. The strain 1 endemic state $E_1$ is GAS under any of the following three sets of conditions:

(i) $R_2 \leq 1$ and $1 \leq \frac{\tilde{\mu}_h}{\mu_h} \leq 1 + \frac{\tilde{\beta}_v}{\mu_v}$;

(ii) $p_1 = p_2$, $\tilde{\beta}_h < \tilde{\beta}_h$, and $\frac{f_1(\tilde{\beta}_h)}{f_1(\tilde{\beta}_h)} \leq 1 + \frac{1}{R_{2+}} - \frac{1}{R_{1+}}$; or

(iii) $p_1 = p_2$, $\tilde{\beta}_h > \tilde{\beta}_h$, and $\left(1 - \frac{f_1(\tilde{\beta}_h)}{f_1(\tilde{\beta}_h)}\right) R_{2+} \leq R_{1+}$,

where $\tilde{\mu}_h = (1 - p_j)\mu_h$, $R_{j+} = \tilde{\beta}_h^j / \mu_h \tilde{\mu}_v$, $f_j(x) = x/(x + \tilde{\mu}_v)$ ($j = 1, 2$). Likewise, the strain 2 endemic state $E_2$ is GAS under any of the following three sets of conditions:

(i) $R_1 \leq 1$ and $1 \leq \frac{\tilde{\mu}_h}{\mu_h} \leq 1 + \frac{\tilde{\beta}_v}{\mu_v}$;

(ii) $p_1 = p_2$, $\tilde{\beta}_h < \tilde{\beta}_h$, and $\left(1 - \frac{f_2(\tilde{\beta}_h)}{f_2(\tilde{\beta}_h)}\right) \frac{R_{1+}}{R_{2+}} \leq \frac{1}{R_{1+}} - \frac{1}{R_{2+}}$; or

(iii) $p_1 = p_2$, $\tilde{\beta}_h > \tilde{\beta}_h$, and $\left(1 - \frac{f_2(\tilde{\beta}_h)}{f_2(\tilde{\beta}_h)}\right) \frac{R_{1+}}{R_{2+}} \leq \frac{1}{R_{1+}} - \frac{1}{R_{2+}}$.

The proofs of these results involve a standard application of Lyapunov functions. We first reintroduce $S_h$ and $S_v$ and normalize the system, dividing through by $N_h$ or $N_v$, as appropriate (e.g. defining $s_h = S_h/N_h$):

$s_h' = \tilde{\mu}_h s_h + \tilde{\beta}_h s_v h_1 - \tilde{\beta}_h h_1 s_1 - \tilde{\beta}_h h_2 s_2$

$i_h' = \tilde{\beta}_h h_2 s_1 - \tilde{\mu}_h i_h + \tilde{\mu}_h s_2 - \tilde{\mu}_h i_2$

$s_v' = \tilde{\mu}_v i_1 + \tilde{\beta}_v s_v h_1 - \tilde{\beta}_v h_1 s_v - \tilde{\beta}_v h_2 s_2$

$i_v' = \tilde{\beta}_v h_2 s_v - \tilde{\mu}_v i_v$

The corresponding Lyapunov function candidate is

$$V = k_0 \left( s_h - s_h^* - s_h^* \log \frac{s_h}{s_h^*} \right) + k_1 \left( i_h - i_h^* - i_h^* \log \frac{i_h}{i_h^*} \right) + k_2 \left( h_2 - h_2^* - h_2^* \log \frac{h_2}{h_2^*} \right) + k_3 \left( s_v - s_v^* - s_v^* \log \frac{s_v}{s_v^*} \right) + k_4 \left( i_v - i_v^* - i_v^* \log \frac{i_v}{i_v^*} \right) + k_5 \left( i_2 - i_2^* - i_2^* \log \frac{i_2}{i_2^*} \right)$$
A.2.1 The disease-free equilibrium (DFE)

Here \( s_0^* = s_1^* = 1, \ i_0^* = i_0^* = i_1^* = i_2^* = 0 \), and (for stability) \( R_{1+} \leq 1 \), \( R_{2+} \leq 1 \), where \( R_{j+} = \tilde{R}_{j+}^{\text{DFE}} / \tilde{\mu}_h \tilde{\mu}_v \) and \( R_{j+} < 1 \iff R_j < 1 \). Then

\[
\frac{dV}{dt} = \left[ k_1 + k_0 \left( 1 - \frac{\mu_h}{\beta_v} \right) \right] \left[ \frac{\beta_h}{\beta_v \sigma_v} (1 - s_v) \right] + \left[ k_2 + k_0 \left( 1 - \frac{\mu_h}{\beta_v} \right) \right] \left[ \frac{\beta_h}{\beta_v \sigma_v} (1 - s_v) \right]
\]

\[
+ \left[ k_4 + k_3 \left( 1 - \frac{\mu_v}{\sigma_v} \right) \right] \left[ \frac{\beta_v}{\beta_h \sigma_h} (1 - s_h) \right] + \left[ k_5 + k_3 \left( 1 - \frac{\mu_v}{\sigma_v} \right) \right] \left[ \frac{\beta_v}{\beta_h \sigma_h} (1 - s_h) \right]
\]

\[
= -k_0 \left( 1 - \frac{\mu_h}{\beta_v} \right) \left( \frac{1}{\beta_v} \mu_h + \frac{1}{\beta_v} \mu_v \right) - \left[ \mu_h (1 - s_v) \right] - \left[ \mu_v (1 - s_h) \right]
\]

\[
- i_1 [k_4 \beta_h (1 - s_v) - k_3 (1 - s_v)] - i_2 [k_3 \beta_v (1 - s_h) - k_2 (1 - s_h)]
\]

The first two of these six terms are clearly non-positive. The third term is non-positive if

\[
k_1 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq k_4 \sigma_v + k_3 (1 - s_v) \quad \text{for all } s_v \in [0, 1], \ i.e. k_1 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq \max(k_3, k_4).
\]

We obtain similar inequalities for the remaining three terms. Thus \( dV/dt < 0 \) if all eight of the following conditions hold:

(i) \( k_1 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq k_4 \), \quad (ii) \( k_2 \frac{\tilde{\mu}_v}{\tilde{\beta}_h} \geq k_1 \), \quad (iii) \( k_2 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq k_5 \), \quad (iv) \( k_3 \frac{\tilde{\mu}_v}{\tilde{\beta}_h} \geq k_2 \), \quad (v) \( k_1 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq k_3 \), \quad (vi) \( k_2 \frac{\tilde{\mu}_v}{\tilde{\beta}_h} \geq k_0 \), \quad (vii) \( k_2 \frac{\tilde{\mu}_h}{\tilde{\beta}_v} \geq k_3 \), \quad (viii) \( k_3 \frac{\tilde{\mu}_v}{\tilde{\beta}_h} \geq k_0 \).

We combine (i) and (ii) and let \( k_1 = 1 \) to get

\[
\frac{\tilde{\mu}_h}{\tilde{\beta}_v} \leq k_4 \frac{\tilde{\mu}_h}{\tilde{\beta}_v}, \quad \text{i.e. } R_{1+} \leq \frac{\tilde{\beta}_h}{\tilde{\mu}_h} k_4 \\leq 1,
\]

which is clearly only possible if \( R_{1+} \leq 1 \). Under this hypothesis, we continue, arbitrarily choosing the upper bound \( k_4 = \tilde{\mu}_h / \tilde{\beta}_v \). We now similarly combine (iii) and (iv) and let \( k_2 = 1 \) to obtain

\[
\frac{\tilde{\mu}_h}{\tilde{\beta}_v} \leq k_5 \frac{\tilde{\mu}_h}{\tilde{\beta}_v}, \quad \text{i.e. } R_{2+} \leq \frac{\tilde{\beta}_h}{\tilde{\mu}_h} k_5 \leq 1,
\]

which is clearly only possible if \( R_{2+} \leq 1 \). Assuming it is, we take \( k_3 = \tilde{\mu}_h / \tilde{\beta}_v \).

Conditions (v) and (vii) now simplify to \( k_3 \leq \min(\tilde{\mu}_h / \tilde{\beta}_v, 1) \), so we choose \( k_3 \) to be the minimum of the two given values. Finally, (vi) and (viii) simplify to \( k_0 \leq \min(1/R_{1+}, 1/R_{2+}) \), so we choose \( k_0 \) to be the smaller of those two values. This makes \( dV/dt < 0 \) everywhere except the DFE, where \( dV/dt = 0 \), so \( V \) is a strong Lyapunov function and the DFE is GAS as long as \( R_0 \leq 1 \ (\iff R_{1+} \leq 1 \text{ and } R_{2+} \leq 1) \).
A.2.2 The endemic equilibria

We first consider $E_1$, for which $s_{h_2}^* = i_{v_2}^* = 0$, $\tilde{\beta}_{h_1} s_{h_1}' v_1^* = \mu_{h_1} s_{h_1}^* + \tilde{\beta}_{v_1} s_{v_1}' i_{v_1}^* = \mu_{v_1} i_{v_1}^* + s_{h_1}^* + i_{v_1}^* = 1$, $s_{v}^* + i_{v}^* = 1$, and $R_{1+} > 1$. Now, since $s_{h} + h_{1} + h_{2} = 1 = s_{h}^* + i_{v}^*$, $h_{1} = -(s_{h} - s_{h}^*) + i_{v} - i_{v}^*$.

We first consider the endemic (strain 1) terms in $dV/dt$:

$$k_0 \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \tilde{\mu}_{h_1} h_{1} = -k_0 \tilde{\mu}_{h_1} \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* - k_0 \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \tilde{\mu}_{h_1} h_{2}$$

and likewise

$$k_3 \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \tilde{\mu}_{v} v_{1} = -k_3 \tilde{\mu}_{v} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \bar{\beta}_{v_1} s_{v_1}' h_{1}^* - k_3 \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \tilde{\mu}_{v_1} v_{2},$$

so that the four strain 1 terms become

$$-k_0 \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* - k_0 \tilde{\mu}_{h_1} h_{1} = k_0 \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* - \bar{\beta}_{h_1} s_{h_1}' v_1^*$$

$$-k_0 \tilde{\mu}_{h_1} \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) h_{1} - k_0 \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) \tilde{\mu}_{h_1} h_{2}$$

$$-k_3 \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \bar{\beta}_{v_1} s_{v_1}' h_{1}^* - k_3 \tilde{\mu}_{v_1} v_{1} = k_3 \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \bar{\beta}_{v_1} s_{v_1}' h_{1}^* - \bar{\beta}_{v_1} s_{v_1}' h_{1}^*$$

$$-k_3 \tilde{\mu}_{v_1} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) v_{1} - k_3 \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) \tilde{\mu}_{v_1} v_{2},$$

where the middle term in each of the last two equations is obtained via the equilibrium conditions. The terms sum to

$$-k_0 \tilde{\mu}_{h_1} \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) h_{1} - k_1 \tilde{\mu}_{h_1} h_{1}$$

$$-k_3 \tilde{\mu}_{v_1} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) v_{1} - k_4 \tilde{\mu}_{v_1} v_{1} + \bar{\beta}_{h_1} s_{h_1}' v_1^* \times Z,$$

where

$$Z = k_0 \left( 1 - \frac{s_{v}^*}{s_{v}} \right) \left( 1 - \frac{s_{h}^*}{s_{h}} \right) + k_1 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{h}^*}{s_{h}} \right) + k_4 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{v}^*}{s_{v}} \right)$$

with $k = \bar{\beta}_{h_1} s_{h_1}' v_1^* / \bar{\beta}_{v_1} s_{v_1}' h_{1}^*$. To simplify, we let $k_0 = k_1$ and $k_3 = k_4 = k_0 k$, so that

$$Z = k_0 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{h}^*}{s_{h}} \right) + 4 \frac{s_{h}^*}{s_{h}} - \frac{s_{v}^*}{s_{v}} = \frac{i_{v}^*}{i_{v}} \left( \frac{s_{h}^*}{s_{h}} \right) - \frac{i_{v}^*}{i_{v}} \left( \frac{s_{v}^*}{s_{v}} \right).$$

The first two terms, multiplied by the coefficient of $Z$ in $dV/dt$, become

$$k_0 \bar{\beta}_{h_1} s_{h_1}' v_1^* \left( \frac{i_{v}^*}{i_{v}} \right) \frac{i_{v}^*}{i_{v}} \left( \frac{s_{h}^*}{s_{h}} \right) = k_0 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* + \bar{\beta}_{v_1} s_{v_1}' h_{1}^*$$

$$= k_0 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* + \bar{\beta}_{v_1} s_{v_1}' h_{1}^*$$

$$= k_0 \left( \frac{i_{v}^*}{i_{v}} \right) \left( \frac{s_{h}^*}{s_{h}} \right) \bar{\beta}_{h_1} s_{h_1}' v_1^* + \bar{\beta}_{v_1} s_{v_1}' h_{1}^*$$

thereby cancelling with the two identical terms in $dV/dt$, and leaving the endemic terms' sum as

$$-k_0 \tilde{\mu}_{h_1} \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) - k_0 \tilde{\mu}_{h_1} \left( \frac{s_{h} - s_{h}^*}{s_{h}} \right) - k_3 \tilde{\mu}_{v_1} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) - k_3 \tilde{\mu}_{v_1} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) - k_4 \tilde{\mu}_{v_1} \left( \frac{s_{v} - s_{v}^*}{s_{v}} \right) - 4 k_0 \tilde{\mu}_{h_1} \bar{\beta}_{h_1} s_{h_1}' v_1^* \left( G - A \right),$$

where $G$ and $A$ are the geometric and arithmetic means, respectively, of the four quantities $s_{h}^*/s_{h}$, $s_{v}^*/s_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$, $i_{v}^*/i_{v}$. By the AM–GM inequality, $A \geq G$, with equality iff all four quantities are equal.
We now consider the strain 2 terms (recalling \( \tilde{n}_{h2} = r_{i2} = 0 \)): 

\[
\begin{align*}
[k_2 - k_0 \left( \frac{s_h - s_h^*}{s_h} \right) ] [\tilde{\beta}_{h2}\tilde{n}_i 
& \leq k_3 \left( \frac{k_v - s_v^*}{s_v} \right) ] [\tilde{\beta}_{r2}r_i - \tilde{\mu}_v 
& = k_0 \left( \frac{s_h - s_h^*}{s_h} \right) \tilde{\mu}_{h2}h_2 + k_3 \left( \frac{s_v - s_v^*}{s_v} \right) \tilde{\mu}_v r_i 
& - r_i (k_3 \tilde{\mu}_v + k_0 \tilde{\beta}_{h2}h_2^* - \tilde{\mu}_{h2}(k_2 \tilde{\beta}_{h2} + k_3 \tilde{\beta}_{r2}r_1^* - \tilde{\beta}_{r2}(k_3 s_v + k_3 (1 - s_v))))
\end{align*}
\]

The coefficients of \( \tilde{n}_h \) and \( r_i \) in the last two terms are non-positive for all \( s_\nu \in [0, 1] \) and all \( s_h \in [0, 1] \), respectively, iff 

\[
k_2 \tilde{\mu}_{h2} \tilde{\beta}_{r2} + k_3 r_i^* \geq \max(k_5, k_3) \quad \text{and} \quad k_5 \tilde{\mu}_v \tilde{\beta}_{h2} + k_0 r_i^* \geq \max(k_2, k_0);
\]

these conditions can be expanded and separated as

\[
i (i) \quad k_3 \leq \frac{k_{h2}}{k_2} \frac{\tilde{\mu}_{h2} \tilde{\beta}_{r2}}{k_{h2} s_v^*}, \quad (ii) \quad k_5 \leq \frac{k_{h2} \tilde{\beta}_{v2} k_i^*}{k_{h2} s_v}, \quad (iii) \quad \frac{\tilde{\beta}_{h2} \tilde{\beta}_{v1} (1 - k_0 r_i^*)}{\tilde{\mu}_v} \leq \frac{k_5}{k_2} \tilde{\mu}_v \quad (iv) \quad k_0 \leq k_5 \frac{\tilde{\mu}_v}{\tilde{\beta}_{h2} s_h^*}.
\]

We can simplify somewhat by setting \( k_2 = 1 \) and recalling \( k_3 = k_0 k_1 \):

\[
i (i) \quad k_0 \leq \frac{\tilde{\mu}_h}{\tilde{\beta}_{h2} k_i^*}, \quad (ii) \quad k_5 \leq \frac{\tilde{\mu}_h}{\tilde{\beta}_{h2}} + k_0 k_i^* \tilde{\nu}_1, \quad (iii) \quad \frac{\tilde{\beta}_{h2} \tilde{\beta}_{v1} (1 - k_0 r_i^*)}{\tilde{\mu}_v} \leq \frac{k_5}{k_2} \tilde{\mu}_v \quad (iv) \quad k_0 \leq k_5 \frac{\tilde{\mu}_v}{\tilde{\beta}_{h2} s_h^*}.
\]

Using

\[
k = \frac{\tilde{\mu}_h r_i^* \tilde{\beta}_{h1}}{\tilde{\nu}_1 \tilde{\beta}_{v1}}, \quad i^*_h = \frac{\tilde{\beta}_{h1} \tilde{\beta}_{v1} - \tilde{\mu}_h \tilde{\nu}_1}{\tilde{\beta}_{v1} (\tilde{\beta}_{h1} + \tilde{\mu}_h)}, \quad i^*_v = \frac{\tilde{\beta}_{h1} \tilde{\beta}_{v1} - \tilde{\mu}_h \tilde{\mu}_v}{\tilde{\beta}_{h1} (\tilde{\beta}_{v1} + \tilde{\mu}_v)}
\]

and

\[
x^*_h = \frac{\tilde{\nu}_1 \tilde{\beta}_{h1}}{\tilde{\beta}_{v1} (\tilde{\beta}_{h1} + \tilde{\mu}_h)}
\]

we can further simplify (i) to provide the following upper bound for \( k_0 \):

\[
k_0 \leq \frac{\tilde{\beta}_{v1} \tilde{\nu}_1 \tilde{\beta}_{h2}}{\tilde{\beta}_{h1} \tilde{\beta}_{v2}}.
\]

The remaining conditions bound \( k_5 \) in terms of \( k_0 \). Satisfying both (ii) and (iii):

\[
\frac{\tilde{\beta}_{h2} \tilde{\beta}_{v1} (1 - k_0 r_i^*)_{h1}}{\tilde{\mu}_v} \leq k_5 \leq \frac{\tilde{\mu}_h}{\tilde{\beta}_{h2}} + k_0 k_i^* \tilde{\nu}_1
\]

is only possible if

\[
\frac{\tilde{\beta}_{h2} \tilde{\beta}_{v1} (1 - k_0 r_i^*)_{h1}}{\tilde{\mu}_v} \leq \frac{\tilde{\mu}_h}{\tilde{\beta}_{h2}} + k_0 k_i^* \tilde{\nu}_1, \quad \text{i.e.} \quad 1 \leq \frac{1}{R_{2+}} + k_0 \left( i^*_h + k_i^* \frac{\tilde{\mu}_v}{\tilde{\beta}_{h2}} \right)
\]

Clearly \( R_{2+} \leq 1 \) is enough to satisfy this, but we can do better:

\[
1 \leq \frac{1}{R_{2+}} + k_0 \left( i^*_h + k_i^* \frac{\tilde{\mu}_v}{\tilde{\beta}_{h2}} \right) = \frac{1}{R_{2+}} + k_0 \tilde{r}_h \left( 1 + k_i^* \frac{\tilde{\mu}_v}{\tilde{\beta}_{h2}} \right) \equiv F.
\]

Substituting the equilibrium value

\[
i^*_h = \frac{\tilde{\beta}_{h1} \tilde{\beta}_{v1} - \tilde{\mu}_h \tilde{\nu}_1}{\tilde{\beta}_{v1} (\tilde{\beta}_{h1} + \tilde{\mu}_h)} = \left( 1 - \frac{1}{R_{1+}} \right) \frac{\tilde{\beta}_{h1}}{\tilde{\beta}_{h1} + \tilde{\mu}_h},
\]

\[
F = \frac{1}{R_{2+}} + k_0 \left( 1 - \frac{1}{R_{1+}} \right) \frac{f(\tilde{\beta}_{h1})}{f(\tilde{\beta}_{h2})}, \quad \text{where} \quad f(x) = \frac{x}{x + \tilde{\mu}_h}.
\]

The condition \( F \geq 1 \) which enables (ii) and (iii) to be satisfied (by suitable choice of \( k_5 \)) is itself satisfied if \( R_{2+} \leq R_{1+} \) and \( k_0 \geq f(\tilde{\beta}_{h2}) f(\tilde{\beta}_{h1}) (\ast) \), since \( R_{2+} \leq R_{1+} \Rightarrow 1/R_{2+} \geq 1/R_{1+} \), so that

\[
F \geq \frac{1}{R_{1+}} + \left[ \frac{k_0 f(\tilde{\beta}_{h1})}{f(\tilde{\beta}_{h2})} \right] \left( 1 - \frac{1}{R_{1+}} \right) \geq \frac{1}{R_{1+}} + \left( 1 - \frac{1}{R_{1+}} \right) = 1.
\]
This new lower bound (⋆) on \( k_0 \) can be satisfied simultaneously with (i) only if

\[
\frac{f(\bar{\theta}_{h2})}{f(\bar{\theta}_{h1})} = \frac{(\bar{\theta}_{h1} + \bar{\mu}_{h1})\bar{\theta}_{h2}}{(\bar{\theta}_{h2} + \bar{\mu}_{h2})\bar{\theta}_{h1}} \leq \frac{\bar{\beta}_{11}}{\bar{\mu}_{h1}}\frac{\bar{\mu}_{v2}}{\mu_{v}}
\]

\[
\left(\frac{1 - f(\bar{\theta}_{h2})}{1 - f(\bar{\theta}_{h1})}\right) R_{2+} \leq R_{1+}.
\]  

(A2)

Note that if \( \bar{\theta}_{h1} < \bar{\theta}_{h2} \) then \( R_{2+} \leq R_{1+} \) implies Equation (A2), while if \( \bar{\theta}_{h1} > \bar{\theta}_{h2} \) then Equation (A2) implies \( R_{2+} \leq R_{1+} \).

Meanwhile, satisfying (ii) and (iv) simultaneously requires that

\[
\frac{\bar{\theta}_{h2}}{\mu_{v}}(1 - \bar{\eta}_{1})k_0 \leq \frac{\bar{\mu}_{h2}}{\bar{\mu}_{v}} + k_0\bar{\beta}_{11},
\]

which can be simplified to

\[
R_{2+}\left[1 - \left(1 - \frac{1}{R_{1+}}\right)\frac{f(\bar{\theta}_{h1})}{f(\bar{\theta}_{h2})}\right]k_0 \leq 1.
\]

This is satisfied automatically (i.e. for any \( k_0 \)) if \( (1 - 1/R_{1+}) \geq f(\bar{\theta}_{h2})/f(\bar{\theta}_{h1}) \); otherwise it becomes

\[
k_0 \leq \frac{1}{R_{2+}[1 - (1 - 1/R_{1+})f(\bar{\theta}_{h1})/f(\bar{\theta}_{h2})]}.
\]  

(A3)

The bounds (⋆) and (A3) can be satisfied simultaneously iff \( (1 - 1/R_{1+}) \geq f(\bar{\theta}_{h2})/f(\bar{\theta}_{h1}) \) (⋆⋆) or

\[
\frac{f(\bar{\theta}_{h2})}{f(\bar{\theta}_{h1})} \leq \frac{1}{R_{2+}[1 - (1 - 1/R_{1+})(f(\bar{\theta}_{h1})/f(\bar{\theta}_{h2}))]}
\]

\[
\left[1 - \left(1 - \frac{1}{R_{1+}}\right)\frac{f(\bar{\theta}_{h1})}{f(\bar{\theta}_{h2})}\right] \leq \frac{1}{R_{2+}}
\]

\[
\frac{f(\bar{\theta}_{h2})}{f(\bar{\theta}_{h1})} \leq 1 + \frac{1}{R_{2+}} - \frac{1}{R_{1+}}.
\]  

(A4)

Note first that (⋆⋆) or (A4) simplifies to just (A4). Note also that if \( \bar{\theta}_{h1} > \bar{\theta}_{h2} \) then \( R_{2+} \leq R_{1+} \) implies (A4), while if \( \bar{\theta}_{h1} < \bar{\theta}_{h2} \) then (A4) implies \( R_{2+} \leq R_{1+} \).

To put everything together, we have, finally, that

\[
\frac{dV}{dt} = -k_0\bar{\mu}_{h1}\left(\frac{s_h - s_h^\star}{s_h}\right)^2 - k_0\bar{k}\bar{\mu}_{v}\left(\frac{s_v - s_v^\star}{s_v}\right)^2 + 4k_0\bar{\beta}_{h1}s_h^\star e_{h1}(G - A)
\]

\[-k_0\left(\frac{s_h - s_h^\star}{s_h}\right)(\bar{\mu}_{h1} - \bar{\mu}_{h2})h_2
\]

\[-i_{h2}[\bar{\mu}_{h2} + k_0\bar{\beta}_{h2}e_{h2}] - \bar{\nu}_v(5s_v + k_0(1 - s_v)) - i_{h2}[5\bar{\beta}_{h1} + k_0\bar{\beta}_{h2}e_{h1} - \bar{\theta}_{h2}s_h + k_0(1 - s_h)].
\]

The terms in the first line are all negative. The terms in the last line are negative if conditions (i)–(iv) hold, which can be accomplished in several ways, including:

- \( R_{2+} \leq 1 \) (and judicious choice of \( k_0 \) and \( k_3 \));
- \( R_{2+} \leq R_{1+} \), (A2), and (A4) (and judicious choice of \( k_0 \) and \( k_3 \)).

From the implications identified earlier, the latter set of criteria simplifies to

- either \( \bar{\theta}_{h1} < \bar{\theta}_{h2} \) and (A4), or \( \bar{\theta}_{h1} > \bar{\theta}_{h2} \) and (A2).

The term in the middle line, however, may be of either sign, and potentially very large, without further constraints. Thus, in general, we require that \( \bar{\mu}_{h1} = \bar{\mu}_{h2} \) (i.e. that \( p_1 = p_2 \)), except under the more restrictive hypothesis \( R_{2+} \leq 1 \), in
which case the term $-k_0 h_t k \beta_2 v_1^*$ can be used to counterbalance this other term:

$$-k_0 \left( \frac{s_h - s_h^*}{s_h} \right) (\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}) h_2 - k_0 h_t k \beta_2 v_1^* \leq 0$$

$$\left( \frac{s_h - s_h^*}{s_h} \right) (\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}) + k \beta_2 v_1^* \geq 0$$

$$(s_h - s_h^*)(\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}) + \frac{s_h \tilde{\mu}_{h_1} \beta_2 v_1^*}{\mu_v} \geq 0$$

$$s_h \left[ (\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}) + \frac{\tilde{\mu}_{h_1} \beta_2 v_1^*}{\mu_v} \right] \geq s_h^* (\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}).$$

Since the left-hand side is linear in $s_h$, the inequality above holds for all $s_h \in [0, 1]$ iff it holds for $s_h = 0$ and for $s_h = 1$. It clearly holds for $s_h = 0$ iff $\tilde{\mu}_{h_1} \leq \tilde{\mu}_{h_2}$. It holds for $s_h = 1$ iff

$$(\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2}) + \frac{\tilde{\mu}_{h_1} \beta_2 v_1^*}{\mu_v} \geq s_h^* (\tilde{\mu}_{h_1} - \tilde{\mu}_{h_2})$$

$$\frac{\tilde{\mu}_{h_1} \beta_2 v_1^*}{\mu_v} \geq (1 - s_h^*)(\tilde{\mu}_{h_2} - \tilde{\mu}_{h_1}) = (\tilde{\mu}_{h_2} - \tilde{\mu}_{h_1}) s_h^*$$

$$\tilde{\mu}_{h_1} \left( 1 + \frac{\tilde{\beta}_2}{\mu_v} \right) \geq \tilde{\mu}_{h_2}.$$

Thus it holds for all $s_h \in [0, 1]$ iff

$$1 \leq \frac{\tilde{\mu}_{h_2}}{\tilde{\mu}_{h_1}} \leq 1 + \frac{\tilde{\beta}_2}{\mu_v}. \quad (A5)$$

Hence, finally, we can conclude that $dV/dt < 0$ everywhere except at the equilibrium $E_1$, which is therefore GAS, if $(R_{1+} \geq 1)$ and either:

- $R_{2+} \leq 1$ and (A5); or
- $p = p_2$, and either $\hat{\beta}_{h_1} < \hat{\beta}_{h_2}$ and (A4), or $\hat{\beta}_{h_1} > \hat{\beta}_{h_2}$ and (A2).