Graphical analysis of evolutionary trade-off in sylvatic *Trypanosoma cruzi* transmission modes

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Abstract

Evolutionary trade-off (one attribute increasing at the expense of another) is a central notion in the evolution of traits, well-studied especially in life-history theory, where a framework first developed by Levins illustrates how internal (genetics) and external (fitness landscapes) forces interact to shape an organism's ongoing adaptation. This manuscript extends this framework to the context of vector-borne pathogens, with the example of *Trypanosoma cruzi* (the etiological agent of Chagas' disease) adapting via trade-off among three different infection routes to hosts—stercorarian, vertical, and oral—in response to an epidemiological landscape that involves both hosts and vectors. Using a fitness measure derived from an invasion reproductive number, this study analyzes several different trade-off scenarios in cycles involving raccoons or woodrats, and finds that selection favors oral transmission to raccoons but classical stercorarian transmission to woodrats even under the same predation rate, with vertical (congenital) transmission favored only when aligned with dominant oral transmission or (at trace levels) under a weak trade-off.

1 Introduction

Evolution is well-known to involve trade-offs: because of internal constraints (genetic or eco-physiological) an increase in one trait often comes at the expense of another. The study of how such trade-offs occur and shape organisms' overall ability to survive and reproduce in a given environment has a long history in the scientific literature. Within this body of research, the landscape on which this evolutionary trade-off occurs has come to be described in terms of maximizing fitness, measured by a single function which incorporates all of an organism's traits relative to survival and reproduction of the species. In population genetics, both the traits and the associated fitness measure are quantified mathematically, in order to describe the evolutionary process as well as the point (a local, if not global, optimum) which attains the highest possible fitness given the trade-off constraint inherent to adaptation between two given traits ([17, 24, 25] and references within).

Levins [17] introduced a framework for modeling this process of adaptation between two traits and the influence of environment in shaping it. Levins's graphical approach, widely applied and influential, distinguishes internal (population genetic) and external (environment-mediated fitness) forces by representing both as curves in trait space: the trade-off curve in the former case, and level curves (contours) for the fitness measure in the latter. The highest contour to intersect the trade-off curve identifies the optimal combination of traits (where the curves touch) toward which evolution points. To describe how two traits vary with regard to each other, Levins gave a shape (the trade-off curve) to the set of feasible combinations called the "fitness set." Trade-offs described by a curve which is concave down, called weak trade-offs, have specialists (those at either extreme, with one trait fully developed and the other absent) gain more in a new trait through mutation

than they lose in the dominant trait; concave up trade-off curves, called strong trade-offs, cause specialists to lose more of their dominant trait initially in evolution than they gain in the other trait (cf. Figure 1). Levins originated the idea that weak trade-offs favor generalists (individuals with both traits partly developed) while strong trade-offs favor specialists. Levins’s approach has been applied successfully in life-history theory, notably to describe the evolution of reproductive effort (iteroparity vs. semelparity) [24].

Rueffler *et al.* [24, 25] extend this framework by questioning the assumption of frequency independence made in Levins’s approach, which leads “to the intrinsic rate of increase r as the natural optimization criterion,” a quantity independent of the frequency of the resident organism being invaded by the mutant. Rueffler *et al.* add [24] that studies which have incorporated density dependence (one alternative to complete frequency independence) “mostly used either the expected lifetime reproductive success R_0 or population size at equilibrium $\hat{N}$ as the optimization criteria” (p. 166). They study instead frequency-dependent fitness measures, where the frequency of resident trait combinations affects a mutant’s ability to invade. Their context recasts Levins’s original notion of reproduction taking place in two distinct environments (each trait representing reproductive ability in a different environment) as “a consumer feeding on two nutritionally substitutable resources” [25, p. 82]. The present study proposes a further extension of this approach, to a complex epidemiological landscape where notions of frequency and density dependence take on added dimensions.

The evolution of virulence and transmissibility for directly-transmitted pathogens has also been well-studied in epidemiological literature. A central but still controversial theory in pathogen evolution articulates a trade-off between virulence (damage to infected hosts) and host-to-host transmission, in that pathogens which replicate too rapidly within a host may kill the host before the pathogen can be transmitted to other hosts, whereas pathogens that do not induce high mortality can be expected to be transmitted by the host over a longer period of time (albeit at a lower rate), e.g., [3, 1]. Such a trade-off predicts that pathogens will evolve toward an optimal, nonzero virulence which maximizes the pathogen’s overall reproduction between hosts. (The debate over this hypothesis centers around the assumed correlation of both virulence [as differential host mortality] and host-to-host transmission to within-host pathogen replication, for which supporting empirical data are limited, e.g., [10].) Alizon and van Baalen [2] used an embedded model (within-host dynamics linked to population-level dynamics) to study this hypothesis in the context of a vector-borne disease (namely, malaria). Their results support both the existence of the trade-off and the notion that its nature may vary highly from one system to another: for instance, low malaria virulence despite the conventional wisdom that vector-borne pathogens evolve to higher virulence than directly-transmitted ones.

Another important trade-off in pathogen evolution is that between horizontal and vertical transmissibility [18, 8]. For directly transmitted pathogens, horizontal transmission refers to classical host-to-host infectious contacts; vertical, or congenital, transmission occurs in placental mammals when an infected mother passes a pathogen to her offspring during pregnancy. This trade-off builds on the postulated correlation between virulence and horizontal transmission, finding that more virulent—and hence more horizontally transmissible—strains should be favored when hosts are numerous, and less virulent strains—which, being less harmful to hosts, may make vertical transmission more successful—when hosts are scarce [26]. In this way, host density may shape the coevolution of horizontal and vertical pathogen transmissibility, by changing the epidemiological landscape. The present study investigates a similar trade-off between transmission modes in the context of a vector-borne disease, where, although horizontal transmission rates depend on vector density, the vertical route bypasses the vector altogether.

The protozoan parasite *Trypanosoma cruzi*, known as the etiological agent of Chagas’ disease

throughout the Americas, presents an interesting case study in pathogen adaptation because of its many different zoonotic transmission cycles (involving dozens of triatomine vector species and over 100 mammalian host species). Vectors become infected by drawing blood from infected hosts, and the parasite completes its life cycle in the gut of the vector. Hosts are typically infected via stercorarian transmission (contamination of the bite wound with vector feces) following vector bloodmeals, but in some cycles vertical (congenital) and oral (via opportunistic host predation on infected vectors) transmission play important roles. Six different strains (I–VI) of the parasite are recognized, each with its own characteristics. In the southeastern United States through to Texas and northern Mexico, *T. cruzi* I and IV are enzootic in various transmission cycles, with the cross-immunity induced in hosts (see, e.g., [16]) creating interstrain competition for access to them. The primary vector species, *Triatoma sanguisuga* and (in Texas and northern Mexico) *Triatoma gerstaeckeri* are known to be relatively timid (biting hosts from the side rather than on top) and have a long delay (on the order of 30 minutes as opposed to 5 or less) between feeding and defecation, both behaviors making them poor prospects for stercorarian infection [21]. At the same time, raccoons (*Procyon lotor*) there are found infected almost exclusively with *T. cruzi* IV, at a high prevalence (typically 50% or higher) [22]; *T. cruzi* I persists primarily in opossums (*Didelphis marsupialis*) in the southeastern United States (SE US), who are immune to *T. cruzi* IV [23]. In Texas and northern Mexico, meanwhile, both strains are found at roughly equal levels in woodrats (*Neotoma micropus*) [4]. *T. cruzi* I is often described as chagasic and more virulent (see, e.g., [19]) compared to *T. cruzi* IV, which has been found to be better adapted to vertical transmission [11], and the importance of vertical and oral transmission in an epidemiological landscape where classical stercorarian transmission is disadvantaged almost surely plays a role in mediating interstrain competition here.

Host-vector interactions—in particular, the two distinct contact processes that cause stercorarian and oral infection of hosts—add an extra layer to the epidemiological landscape, extending the framework of Levins to incorporate the densities of not only the parasite but also the hosts and vectors. In the context of *T. cruzi* evolution, the pathogen is the consumer and hosts are the resource. Furthermore, the strains’ differentiated adaptation to different transmission routes makes a single host population act as multiple resources at once, with the vector-host ratio weighting the importance of each transmission route through saturation in the contact processes. The importance of host ecology in mediating the coevolution of parasite transmissibility via multiple infection routes has been recognized [1, p. 251] but little studied, especially in the context of vector-borne pathogens [10]. These additional layers in the fitness landscape take the framework beyond its initial context in a way parallel to Rueffler *et al.*’s studies of frequency dependence. To the author’s knowledge, this is the first study on the coevolution of multiple transmission modes in a vector-borne disease.

The present study, however, limits itself to considering the parasite’s adaptation to different modes of [definitive] host infection only, and makes the simplifying assumption that access to vectors remains constant across strains and mutations. In this context, the adaptive trade-off curve is characteristic of the pathogen, the fitness measure is characteristic of the transmission cycle, and the graphical analysis of their intersection will show how each strain responds to the particular selection pressures on it, adapting in each case to the most advantageous combination of transmissibility traits. For example, different transmission cycles correspond to fitness contours with different slopes, which therefore intersect the [same] trade-off curve at different points, accounting for the persistence of multiple strains.

Sylvatic transmission of *T. cruzi* has been modelled successfully using classical nonlinear dynamical systems [5, 6, 7, 12, 13, 14, 15, 20] to study the roles played in infection dynamics by issues such as contact process saturation, the aforementioned multiple host infection routes, cross-immunity, vector dispersal and migration, and vector-host population dynamics. A deterministic

model of interstrain competition predicts classical competitive exclusion based on the pathogen's reproductive numbers [15, 20], from which a fitness measure can be derived, paralleling the notion of invasion fitness (e.g., [9]). One study identified conditions under which the vector-host density ratio can affect the outcome of the competition between two *T. cruzi* strains [20]; another used an adaptive trade-off framework to estimate trade-off strength and degrees of adaptation to stercorarian, vertical, and oral transmissibility in sylvatic cycles [15] for types I and IV. These estimates suggest that *T. cruzi* IV must be well adapted to both oral and vertical transmissibility, enough to dominate in raccoons even when the rates of both types of potential infection event are low, and in woodrats when these rates are higher (but still consistent with field and lab observations). This study will use this same dynamical systems framework as a basis for describing the epidemiological landscape underlying *T. cruzi* adaptation.

In extending the framework originated by Levins to study evolutionary trade-off in the context of alternative infection routes for this vector-borne pathogen, this article considers several (three-way as well as two-way) trade-off scenarios in order to identify evolutionary mechanisms which promote each transmission route (vertical transmission in particular, which is inherently more limited in its ability to reach new hosts). We begin by summarizing the infection dynamics which give rise to the relevant epidemiological fitness measure, continue by analyzing each trade-off scenario in turn mathematically, and conclude with a synthesis comparing the findings.

2 *T. cruzi* transmission and epidemiological invasion fitness

Sylvatic *T. cruzi* transmission of two strains within a single host-vector cycle can be modeled by a nonlinear dynamical system with differential equations tracking the numbers of hosts and vectors infected with each strain, as well as total population densities [15, 20]. Since hosts' immune responses preclude coinfection, the model predicts competitive exclusion, with outcomes measured by reproductive numbers. The parasite's overall *basic reproductive number* in a two-strain setting takes the form $R_0 = \max(R_1, R_2)$, where R_1 and R_2 are the basic reproductive numbers for each of the two strains, the average numbers of secondary infections produced by the respective strains in hosts if a single host infected with that strain is introduced into an entirely susceptible population. (Anderson and May [3] used a basic reproductive number as a pathogen fitness measure in articulating the virulence/transmission trade-off hypothesis.) If neither strain is able to invade a naive population, then $R_0 < 1$ and the parasite dies out. If, however, each strain would persist on its own ($R_1, R_2 > 1$, which observation suggests is true), then the competition is mediated by each strain's *invasion reproductive number* $\tilde{R}_i$, the average number of secondary infections of the given strain produced in hosts if a single host infected with that strain is introduced into a population where the *other* strain is already resident. One strain persists in the presence of the other if its invasion reproductive number (IRN) exceeds one.

It has been shown for this model [15] that precisely one of the two invasion reproductive numbers exceeds 1 for any set of parameter values where $R_0 > 1$; more specifically, it was shown that (cf. [15, eqn. (8)], [20, Sec. 2.3])

$$\tilde{R}_i > 1 \Leftrightarrow M_i > M_j \Leftrightarrow \tilde{R}_j < 1 \quad (i \neq j),$$

where (cf. [15, Sec. 3.2], [20, Sec. 3.1])

$$M_i = \frac{[\beta_{hi}^*(Q) + \rho_i^*(Q)] \beta_v^*(Q)}{1 - p_i},$$

$\beta_{hi}^*(Q)$ is the stercorarian transmission rate for strain i , $\rho_i^*(Q)$ is the oral transmission rate for strain i (both routes for horizontal infection to hosts), $\beta_v^*(Q)$ is the rate of vector infection, all

Figure 1: Strong, neutral, and weak trade-offs describe the evolutionary relationship between two specialization proportions x and y .

Figure 2: Results of two-way trade-off competition, showing the regions in a - b parameter space in which each specialization is favored for neutral and strong trade-offs, (a) without and (b) with adaptation to oral transmission (AOT) aligned with adaptation to vertical transmission. For neutral trade-offs, the “winner” is the sole ESS; for strong trade-offs, both extremes are ESS, with x^+ separating their basins of evolutionary attraction.

functions of the vector-host density ratio Q , and p_i is the vertical transmission “probability” (really a proportion) for strain i . The definition of invasion reproductive number closely parallels that of *invasion fitness*, given in [24] as “the growth rate of an initially rare mutant in a resident population which is at its ecological equilibrium” [9].

Considering now the parasite’s adaptation to stercorarian, vertical and/or oral transmission to hosts, we can write each of the host infection terms in M as a function of the degree of adaptation to the respective transmission route: $\beta_h^*(Q) = x\beta_{hmax}^*(Q)$, $p = yp_{max}$, $\rho^*(Q) = z\rho_{max}^*(Q)$, with $x, y, z \in [0, 1]$ characteristic of a given parasite strain and the various *max* parameters characteristic to a specific host-vector transmission cycle. Then the fitness measure can likewise be rewritten to emphasize this dependence:

$$M = k \frac{x + az}{1 - by},$$

with positive constants $k = \beta_{hmax}^*(Q)\beta_v^*(Q)$, $a = \rho_{max}^*(Q)/\beta_{hmax}^*(Q)$, and $b = p_{max} \leq 1$, leaving implicit for now the dependence upon Q , which was studied in [20]. Note that a compares the strengths of the two contact-based transmission routes, both functions of Q , while b measures the maximum “efficiency” of vertical transmission (under the implicit assumption that the descendants of a given subset of the host population comprise the same proportion of the population as their forebears). The scaling factor k , independent of parasite adaptation, plays only a trivial role in the analysis that follows.

To study how adaptation to these three transmission routes covaries, we consider three distinct scenarios: (i) adaptation to vertical and oral transmission is linked together, $z = y$ (motivated by semi-anecdotal observations that *T. cruzi* IV is better adapted to both than its competitor); (ii) adaptation to oral transmission z is fixed; (iii) all three adaptations covary in a three-way trade-off. The first two of these scenarios can be treated using a standard two-way trade-off, which shall be extended to three for the last scenario.

3 Analysis

3.1 Stercorarian/vertical transmissibility trade-offs

The hypothesized evolutionary trade-off between stercorarian (horizontal) and vertical transmissibilities x and y can be described by a curve relating the proportions of specialization to the respective modes (Figure 1). In terms of the framework of Rueffler et al. [25], this curve is given by $x^{1/\alpha} + y^{1/\alpha} = 1$, where the tuning parameter $\alpha > 0$ measures trade-off strength. For $\alpha < 1$, the curve is concave down, yielding a so-called weak trade-off; for $\alpha > 1$ the curve is concave up, yielding a strong trade-off. The boundary case $\alpha = 1$ is referred to as a neutral trade-off.

Under the hypothesis that adaptation to oral transmission is aligned with adaptation to vertical transmission, we set $z = y$; under the alternative hypothesis that adaptation to oral transmission is fixed, we instead assign z the value (0.177) estimated in [14, 15]. In order to further reduce the analysis to consider a single variable, we use the trade-off constraint to describe y in terms of x , $y = g(x)$ where $g(x) = (1 - x^{1/\alpha})^\alpha$. Since the resulting problem of optimizing $M(x)$ for general α does not admit closed-form solutions, we consider three representative cases $\alpha = \frac{1}{2}, 1, 2$, corresponding to weak, neutral and strong trade-offs, respectively.

We begin by considering the mathematically simplest case, a neutral trade-off $\alpha = 1$. With no adaptation to oral transmission, $z = 0.177$, we have

$$\frac{\partial M}{\partial x} = k \frac{1 - (az + 1)b}{(1 - b + bx)^2} > 0 \Leftrightarrow (az + 1)b < 1;$$

this condition is independent of x , so that if $(az + 1)b < 1$ then M is increasing in x , and thus has its maximum at $x = 1$, whereas if $(az + 1)b > 1$, then M is decreasing in x , and thus has its maximum at $x = 0$. With adaptation to oral transmission, $z = y$, we have

$$\frac{\partial M}{\partial x} = k \frac{1 - a - b}{(1 - b + bx)^2} > 0 \Leftrightarrow a + b < 1;$$

again, its sign is independent of x , so M has its maximum at $x = 1$ if $a + b < 1$, and at $x = 0$ if $a + b > 1$. The end result, depicted graphically in Figure 2, is that a neutral trade-off in this model favors one specialist (which one depends on the relative maximum strengths of the three transmission modes).

We next consider an example of a strong trade-off, using $\alpha = 2$, so that $g(x) = (1 - \sqrt{x})^2$. In the case without adaptation to oral transmission, we calculate

$$M(x) = k \frac{x + az}{1 - b(1 - \sqrt{x})^2}, \quad \frac{\partial M}{\partial x} = k \frac{bx + (1 + azb - b)\sqrt{x} - azb}{\sqrt{x}[1 - b(1 - \sqrt{x})^2]^2},$$

and

$$\frac{\partial M}{\partial x} > 0 \Leftrightarrow x > x_+ = \frac{1}{4} \left[-\left(\frac{1}{b} + az - 1\right) + \sqrt{\left(\frac{1}{b} + az - 1\right)^2 + 4az} \right]^2.$$

Some straightforward algebra shows that $0 < x_+ < \min(az, 1)$. Thus $M(x)$ decreases from 0 to x_+ and then increases to 1, making the two specialists locally ESS. Which of the two has higher fitness depends on whether $(az + 1)b > 1$ (if so, 0 wins).

With adaptation to oral transmission, meanwhile,

$$M(x) = k \frac{x + a(1 - \sqrt{x})^2}{1 - b(1 - \sqrt{x})^2}, \quad \frac{\partial M}{\partial x} = k \frac{bx + (1 + a - b)\sqrt{x} - a}{\sqrt{x}[1 - b(1 - \sqrt{x})^2]^2},$$

and

$$\frac{\partial M}{\partial x} > 0 \Leftrightarrow x > x_+ = \frac{1}{4} \left[- \left(\frac{1+a}{b} - 1 \right) + \sqrt{\left(\frac{1+a}{b} - 1 \right)^2 + 4 \frac{a}{b}} \right]^2.$$

We can likewise show $0 < x_+ < \min(a/b, 1)$. Thus $M(x)$ decreases from 0 to x_+ and then increases to 1, making the two specialists locally ESS. Which of the two has higher fitness depends on whether $a + b > 1$ (if so, 0 wins).

Looking instead at a weak trade-off, $\alpha = 1/2$, $g(x) = \sqrt{1-x^2}$, without adaptation to oral transmission we have

$$M = k \frac{x + az}{1 - b\sqrt{1-x^2}}, \quad \frac{\partial M}{\partial x} = k \frac{\sqrt{1-x^2} - b - azbx}{\sqrt{1-x^2}(1 - b\sqrt{1-x^2})^2},$$

and

$$\frac{\partial M}{\partial x} > 0 \Leftrightarrow x < x_+ = \frac{-azb^2 + \sqrt{1-b^2+a^2z^2b^2}}{1+a^2z^2b^2}.$$

One can show $x_+ > 0$, so $M(x)$ increases from 0 to x_+ and decreases thereafter, making x_+ the maximum of M on $[0,1]$. Similarly, with adaptation to oral transmission we have

$$M = k \frac{x + a\sqrt{1-x^2}}{1 - b\sqrt{1-x^2}}, \quad \frac{\partial M}{\partial x} = k \frac{\sqrt{1-x^2} - b - ax}{\sqrt{1-x^2}(1 - b\sqrt{1-x^2})^2},$$

and

$$\frac{\partial M}{\partial x} > 0 \Leftrightarrow x < x_+ = \frac{-ab + \sqrt{1-b^2+a^2}}{1+a^2}.$$

Again, $x_+ > 0$ is the global maximum of M on $[0,1]$, and for the weak trade-off the generalist wins.

From a more two-dimensional graphical perspective, we can observe here the nature of the intersection of the evolutionary trade-off curve with the epidemiological fitness measure M within the unit square ($0 \leq x \leq 1$, $0 \leq y \leq 1$). In the scenario without adaptation to oral transmission, $M = k(x + az)/(1 - by)$, so (solving this equation for y) M has a constant value along contours of the form $y = \frac{M-azk}{bM} - \frac{k}{bM}x$, which are (by inspection) lines with negative slope and (since $azk < M$) positive y -intercept. These lines pass through the first quadrant. Likewise, in the scenario with adaptation to oral transmission, $M = k(x + a\sqrt{1-x^2})/(1 - by)$, with contours $y = (M - kx)/(ak + bM)$; these are also lines with negative slope and positive y -intercept. Therefore, given any smooth path describing the trade-off between specializations, the maximum value of M along that path will be either a point at which the path is tangent to a contour line of M , or else one of the two endpoints of the path. This perspective makes it easy to see (cf. Figure 1) that when the path is concave up, corresponding to a strong trade-off, M will always attain its maximum on the path at one of the two endpoints ($x = 0$ if the slope of the contours is shallower than -1 , and $x = 1$ if the slope of the contours is steeper (more negative) than -1), since the highest downward-sloping line to intersect the path will do so at an endpoint. (This is also true of a neutral trade-off.) Meanwhile, when the path is concave down, corresponding to a weak trade-off, M attains a maximum along the path $y = g(x)$ at the point where the slope $g'(x)$ of the path is closest to the slope of the contour lines. Since trade-offs defined by the symmetric form $g(x) = (1 - x^{1/\alpha})^\alpha$ have $g'(0) = 0$ and $g'(x) \rightarrow -\infty$ as $x \rightarrow 1$ for weak trade-offs $\alpha < 1$, there is always a point in between where $g'(x)$ matches the contour slope exactly.

3.2 A note on choice of index variable for limiting cases

Once a trade-off function is given to specify the relation between the two characteristics undergoing trade-off, here x and y , one of the variables is often then used as the index variable through which to study the trade-off. However, such a perspective can generate misleading conclusions in considering limiting values of the trade-off strength, here α . For maximally weak ($\alpha \rightarrow 0$) or strong ($\alpha \rightarrow \infty$) trade-offs, half of the trade-off curve approaches one of the bounds of the index variable. Consequently any results for limiting values lose the ability to distinguish among the points on that half of the curve, since they all share (in the limit) the same x -coordinate ($x = 1$ for $\alpha \rightarrow 0$, and $x = 0$ for $\alpha \rightarrow \infty$).

In general, one often considers characteristics x and y which measure the degree of benefit of certain types enjoyed by an organism; therefore a fitness measure $M(x, y)$ should be an increasing function of both x and y , and this is indeed the case for both measures $M = k(x + az)/(1 - by)$ and $M = k(x + ay)/(1 - bz)$ considered in this study (by inspection). On the unit square, then, the origin (0,0) is the global minimum of $M(x, y)$, while the opposite corner (1,1) is the global maximum. Thus for $\alpha \rightarrow 0$ the generalist winner becomes the midpoint (1,1), while for $\alpha \rightarrow \infty$ the global minimum becomes the midpoint (0,0).

These intuitive results are obfuscated, if not counterindicated altogether, by an analysis that focuses only on the x -coordinate of the fitness measure's maximum or minimum. If one considers the fitness measure M on the trade-off curve $y = g(x)$ as a function of one variable, $M(x)$, and allows the trade-off strength α to vary, then one sees that for $M(0) < M(1)$, as $\alpha \rightarrow 0$ from 1, the generalist winner x_+ decreases from 1 but then turns around and approaches 1 asymptotically. As $\alpha \rightarrow \infty$, the local minimum x_+ increases from 0 but then turns around and returns asymptotically toward 0, so that most starting values of x will experience evolution toward $x = 1$. For $M(0) > M(1)$, meanwhile, as $\alpha \rightarrow 0$ from 1, the generalist winner x_+ increases from 0 to 1 asymptotically. As $\alpha \rightarrow \infty$, the local minimum x_+ decreases from 1 toward 0 asymptotically, so that again most starting values of x will experience evolution toward $x = 1$. All this behavior seems to disadvantage the $x = 0$ extreme in an asymmetric way, but the asymmetry is merely an artifact of the way in which half of the trade-off curve is being compressed into a single point when x is used as the index variable. (The same, of course, would hold if y alone were used.)

A straightforward solution is to use an index variable which is unaffected by variations in trade-off strength. One simple choice is $\Delta = x - y$, which uses an axis rotated halfway between those of x and y , and varies from -1 to 1 as (x, y) varies between (0,1) and (1,0) (cf. Figure 3). Any trade-off curve which requires one variable to decrease (or at least not increase) when the other increases can be expressed as a function of Δ , which allows the fitness measure to remain expressed as a function of a single index variable. Figure 5 compares plots of M vs. x for varying values of α with the corresponding plots of M vs. Δ , for both $M(0) < M(1)$ and $M(0) > M(1)$; in each case, the plots of M vs. x suggest that M is increasing almost everywhere for extreme values of α , but the plots of M vs. Δ show clearly the local extremum approaching the midpoint of the curve as α becomes extreme.

3.3 Three-way trade-off

If we now consider that all three transmission routes to hosts (stercorarian, vertical, and oral) evolve independently, then a three-way trade-off exists among them. This extends the adaptive framework into a third dimension, namely z the degree of adaptation to oral transmission. Evolutionary trade-off can then be described in terms of a surface $x^{1/\alpha} + y^{1/\alpha} + z^{1/\alpha} = 1$, and the fitness measure retains the form $M = k(x + az)/(1 - by)$. As before, constant contours of M are linear, here taking

Figure 3: A trade-off curve can be described in terms of either a component characteristic x or a composite characteristic $\Delta = x - y$. Both perspectives preserve the order of points along the curve (here $x_1 > x_2$, $\Delta_1 > \Delta_2$).

Figure 4: The fitness measure M is maximized where the trade-off curve $y = g(x)$ (solid curve) that describes factors internal to pathogen evolution is tangent to a line (dashed) that represents external environmental factors. Different environments produce contour lines with different slopes, and thus different intersection points; in evolutionary terms, different environments favor different generalists. A weak trade-off is pictured on the left, a strong trade-off on the right.

the form of planes $\frac{k}{M}x + by + \frac{ak}{M}z = 1$, and fitness is maximized by the point on the trade-off surface which touches the highest contour plane.

For neutral and strong trade-offs, $\alpha \geq 1$, the trade-off surface remains concave, so that the maximum fitness occurs at one of the three extremes $(1,0,0)$, $(0,1,0)$ and $(0,0,1)$. However, by inspection $M(0,1,0) = 0$, meaning that a parasite solely able to infect hosts via vertical transmission is bound to lose to any other strain, since it has no capability to invade new hosts, only to propagate itself among the descendants of any host(s) it may already have infected. Instead we consider $M(1,0,0) = k$ and $M(1,0,0) = ak$. Thus, for a neutral or strong trade-off, complete adaptation to stercorarian transmission outcompetes complete adaptation to oral transmission if and only if $a < 1$, while the reverse is true iff $a > 1$. This makes sense given that a measures the maximum oral transmission rate relative to the maximum stercorarian transmission rate.

If, however, we assume a weak trade-off, $\alpha < 1$, then the evolutionary trade-off surface is convex, and the optimal fitness occurs at a point on this surface which is tangent to a plane $\frac{k}{M}x + by + \frac{ak}{M}z = 1$ for some M . To identify this point we use constrained optimization with a Lagrange multiplier, maximizing $M = k \frac{x+az}{1-by}$ subject to the constraint $x^n + y^n + z^n = 1$ ($n = 1/\alpha$). We define the function $F = \frac{x+az}{1-by} + \lambda(x^n + y^n + z^n - 1)$ (λ the Lagrange multiplier) and set the partial derivatives to zero:

$$\frac{\partial F}{\partial x} = \frac{1}{1-by} + \lambda n x^{n-1} = 0 \quad \Rightarrow \quad -\lambda = \frac{1}{(1-by)n x^{n-1}}, \quad (1)$$

$$\frac{\partial F}{\partial y} = \frac{b(x+az)}{(1-by)^2} + \lambda n y^{n-1} = 0 \quad \Rightarrow \quad -\lambda = \frac{b(x+az)}{(1-by)^2 n y^{n-1}}, \quad (2)$$

$$\frac{\partial F}{\partial z} = \frac{a}{1-by} + \lambda n z^{n-1} = 0 \quad \Rightarrow \quad -\lambda = \frac{a}{(1-by)n z^{n-1}}. \quad (3)$$

From (1) and (3), $\frac{1}{(1-by)n x^{n-1}} = \frac{a}{(1-by)n z^{n-1}}$, so that $(z/x)^{n-1} = a$, i.e., $z = a^{\frac{\alpha}{1-\alpha}}x$, and thus

Figure 5: The fitness measure M as a function of x (left) or Δ (right), for (from top to bottom within each plot) $\alpha \rightarrow 0$, $\alpha = 1/3$, $\alpha = 1$, $\alpha = 3$, $\alpha \rightarrow \infty$, with and without adaptation to oral transmission (AOT), for $M(0) < M(1)$ and for $M(0) > M(1)$

$az = a^{\frac{1}{1-\alpha}}x$. From (1) and (2), $\frac{1}{(1-by)nx^{n-1}} = \frac{b(x+az)}{(1-by)^{2ny^{n-1}}}$; substituting in the above expression for z and solving for x yields

$$x^n = \frac{\left(\frac{1}{b} - y\right) y^{n-1}}{1 + a^{\frac{1}{1-\alpha}}}.$$

Now

$$z^n = a^{\frac{\alpha}{1-\alpha}} n x^n = a^{\frac{1}{1-\alpha}} \frac{\left(\frac{1}{b} - y\right) y^{n-1}}{1 + a^{\frac{1}{1-\alpha}}},$$

so that the constraint becomes

$$x^n + y^n + z^n = \left(\frac{1}{b} - y\right) y^{n-1} + y^n = y^{n-1}/b = 1.$$

Hence $y = b^{\frac{1}{n-1}} = b^{\frac{\alpha}{1-\alpha}}$, and back-substituting yields $x^n = \frac{1 - b^{\frac{1}{1-\alpha}}}{1 + a^{\frac{1}{1-\alpha}}}$, so that

$$x = \left(\frac{1 - b^{\frac{1}{1-\alpha}}}{1 + a^{\frac{1}{1-\alpha}}}\right)^{\alpha}, \quad z = \left(\frac{a^{\frac{1}{1-\alpha}}}{1 + a^{\frac{1}{1-\alpha}}}\right)^{\alpha} \left(1 - b^{\frac{1}{1-\alpha}}\right)^{\alpha}.$$

Thus weak trade-offs still favor a generalist, so that under a three-way trade-off the only way for vertical transmissibility to survive is a weak trade-off.

3.4 Synthesis

We can compare the results for all three scenarios numerically, by considering the estimates made in [15]. The calculations in the appendix of [15] estimate the trade-off shape to be close to neutral, most likely weak but with a slightly strong trade-off at the upper end of the possibilities. Thus four overall combinations combining trade-off shape with host (or transmission cycle) may be considered, and three scenarios within each such combination: adaptation to oral transmission (i) aligned with that to vertical transmission, (ii) fixed, or (iii) independent of adaptation to vertical or stercorarian transmission (three-way trade-off). Table 1 summarizes the details of all twelve resulting combinations. For woodrats, oral transmission never dominates stercorarian, so vertical transmission persists at more than trace levels only when coupled to oral transmission under a weak trade-off, where a generalist is favored. However, for raccoons oral transmission dominates stercorarian, so vertical transmission is highly favored when coupled with oral (regardless of trade-off strength), and adaptation selects for stercorarian transmission only against vertical, when oral transmissibility is fixed. Finally, we note that for opossums vertical transmission plays no role since they are marsupial rather than placental, which obviates further discussion of their transmission cycle with regard to this trade-off.

4 Discussion

Levins's notion of "fitness set" originated to describe evolutionary trade-off in a population genetics context, where a species varies in its abilities to reproduce in two different environments. This study considers an extension of this notion to the transmission of vector-borne pathogens seeking access to hosts, with reproduction in different environments recast in terms of different transmission routes to a host. In particular, transmission of *Trypanosoma cruzi* to sylvatic hosts involves a combination of stercorarian, vertical, and oral infection, with each parasite strain differentially adapted in regard to each transmission route; the cross-immunity which hosts develop through their immune response creates a competition between strains. The dynamical system used to model this competition predicts classical competitive exclusion and provides a fitness measure via the invasion reproductive number, consistent with studies in life-history theory and pathogen evolution.

Host	Trade-off	Constraint	x	y	z
raccoons	weak	$z = y$ (AOT)	0.006556	0.99747	0.99747
	$(\alpha = 0.862,$	$z = 0.177$ (fixed)	0.999992	4.59×10^{-5}	0.177
	$a = 1.9, b = 0.15)$	none (indep.)	0.017999	7.14×10^{-6}	0.99184
raccoons	strong	$z = y$ (AOT)	0	1	1
	$(\alpha = 1.09,$	$z = 0.177$ (fixed)	1	0	0.177
	$a = 1.55, b = 0.3)$	none (indep.)	0	0	1
woodrats	weak	$z = y$ (AOT)	0.950016	0.085598	0.085598
	$(\alpha = 0.862,$	$z = 0.177$ (fixed)	0.999998	1.39×10^{-5}	0.177
	$a = 0.529, b = 0.15)$	none (indep.)	0.991535	7.14×10^{-6}	0.018574
woodrats	strong	$z = y$ (AOT)	1	0	0
	$(\alpha = 1.09,$	$z = 0.177$ (fixed)	1	0	0.177
	$a = 0.401, b = 0.3)$	none (indep.)	1	0	0

Table 1: A summary of the numerical scenarios (and resulting optimal adaptations (x, y, z)) based on estimates developed in [15]. The optimal adaptation involves almost purely stercorarian transmission ($x \approx 1$) for woodrats but varies more for raccoons.

A comparison between the two *T. cruzi* strains native to the southern United States motivated a study of trade-off between classical stercorarian infectivity and vertical, as well as possibly oral, infectivity applying Levins’s framework as mediated by Rueffler *et al.*, with one strain (*T. cruzi* IV) reportedly better adapted to vertical and oral transmission, and less adapted to stercorarian infectivity, than the other (*T. cruzi* I). The graphical analysis showing the intersection of the trade-off curve (Levins’s “fitness set”) with the contour lines for the fitness measure illustrate here how the evolutionary process (embodied by the constraint $y = g(x)$) interacts with the epidemiological landscape established by the host-vector cycle (the set of level curves of M). The pathogen’s evolution is thus shaped simultaneously by both sets of factors.

Although on one level the results resemble those of studies which assume frequency independence, in that the IRN and resulting fitness measure are independent of the specific characteristics of the hypothetical *resident* pathogen strain, they add a dependence on the vector-host ratio (part of the epidemiological fitness landscape) which weights the importance of the different transmission routes, as anticipated by [1]. The importance of contact process saturation (also suggested by [10]) in this weighting was seen in [20], where the contact process (leading to either stercorarian or oral transmission) whose saturation threshold was closer to the actual vector-host ratio was advantaged. The results of the present study highlight the difference in nature of the trade-off between horizontal host-vector transmission modes and vertical transmission in hosts, which bypasses vectors altogether.

Although Rueffler *et al.* cite [25] a body of empirical studies suggesting that trade-offs are strong in general, both the rough (and considerably less sophisticated) estimates developed in [15] and the observed different abilities of both strains to infect hosts in both (stercorarian and vertical) ways suggest a slightly weak trade-off in this context, capable of leading to different generalist strains surviving on different epidemiological landscapes (transmission cycles). The different hosts (opossums vs. raccoons) in which *T. cruzi* I and IV (respectively) persist offer different epidemiological landscapes, leading to fitness contour lines with different slopes, which therefore intersect the evolution curve at different points, leading the parasite to adapt differently (cf. Figure 4). In the case of *T. cruzi* in the SE US, strain IV is completely shut out of the cycle involving opossums (since they are immune to it), and thus is affected only by the parameters of the cycle involving

raccoons; we may imagine strain IV to have evolved toward the point on the adaptive curve which maximizes the fitness measure of that cycle. Meanwhile, strain I is outcompeted in this cycle but dominates the cycle involving opossums, so we may imagine it to have evolved toward the point on the adaptive curve which maximizes the fitness measure of this latter cycle instead. (For example, the optimal adaptation for the first scenario in Table 1 represents the trade-off curve’s intersection with a fitness contour of slope -0.45 ; the actual value of $x = 0.43$ estimated for *T. cruzi* IV in [15] corresponds to a slope of -0.93 , and the value of $x = 0.75$ for *T. cruzi* I to a slope of -1.14 . Complete adaptation to stercorarian transmission corresponds to a vertical slope, and *T. cruzi* I reflects the influence of such selection in transmission cycles involving opossums or woodrats.)

If instead we assume that all three types of infectivity covary separately, with a three-dimensional trade-off governing adaptation, then vertical transmission, which is unable to access new host lines, survives as part of the optimal trait profile only under a weak trade-off, since strong and neutral trade-offs favor pure specialists, and exclusively vertical transmission leads to diminishing returns in a bounded population. Under a strong trade-off, the rough estimates developed in [15] suggest oral transmission alone outcompetes stercorarian transmission in raccoons, accounting for the dominance of *T. cruzi* IV in that host, while stercorarian transmission may dominate in woodrat populations. Adaptation toward vertical transmission, therefore, implies either a weak trade-off or association of vertical and oral transmission.

Comparison of several different trade-off scenarios suggests that for *T. cruzi* selection pressure encourages vertical transmissibility only when linked to oral transmissibility, or in great moderation (more or less trace levels) under a weak trade-off. Adaptive pressure favors oral transmissibility consistently for raccoons, however, creating a path to dominance for *T. cruzi* IV in related transmission cycles, while woodrat cycles appear to favor classical stercorarian transmission. This result offers some parallel to the notion that for directly-transmitted pathogens horizontal transmission may be favored among high-density hosts, since a significant difference between raccoons and woodrats here is the much higher population density of woodrats; the relative sparseness of raccoon populations may encourage pathogens able to transmit effectively through vertical and/or oral routes.

Finally, although this study of adaptive trade-off was motivated by outright competition between two distinct extant strains of pathogen, the general approach used here applies equally well to other vector-borne pathogens, extending the study of evolution’s interaction with fitness landscapes to an epidemiological context. What remains to be developed (in addition to more rigorous quantitative measures of the specific epidemiological fitness landscapes represented by the *T. cruzi* transmission cycles discussed here) is a better sense of how different infection routes to the same host represent different reproductive environments in a different way than multiple host populations would, as well as how simultaneous competition for access to vectors as well as hosts would complicate this landscape, since this study considers only pathogen adaptation as regards access to hosts.

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