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Mathematical Models of Human African Trypanosomiasis Epidemiology

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Abstract

Human African trypanosomiasis (HAT), commonly called sleeping sickness, is caused by *Trypanosoma* spp. and transmitted by tsetse flies (*Glossina* spp). HAT is usually fatal if untreated and transmission occurs in foci across sub-Saharan Africa. Mathematical modelling of HAT began in the 1980s with extensions of the Ross-Macdonald malaria model and has since consisted, with a few exceptions, of similar deterministic compartmental models. These models have captured the main features of HAT epidemiology and provided insight on the effectiveness of the two main control interventions (treatment of humans and tsetse fly control) in eliminating transmission. However, most existing models have overestimated prevalence of infection and ignored transient dynamics. There is a need for properly validated models, evolving with improved data collection, that can provide quantitative predictions to help guide control and elimination strategies for HAT.

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Contents

1 Introduction

Tsetse flies (*Glossina* spp.) transmit pathogens of the species *Trypanosoma* which can cause African trypanosomiasis in humans and livestock, across approximately 10 million square kilometres of sub-Saharan Africa. Human African trypanosomiasis (HAT), commonly called sleeping sickness, comprises two diseases caused by either *Trypanosoma brucei gambiense* (Gambian HAT) or *T. b. rhodesiense* (Rhodesian HAT). Animal African trypanosomiasis (AAT), also known as nagana, is predominantly caused by *T. congolense* and *T. vivax*.

Generally, HAT is fatal if untreated; similarly AAT is fatal to some livestock species, particularly more productive breeds exotic to Africa, and has a significant impact on the productivity of indigenous animals. Although this group of tsetse-borne pathogens is found only in sub-Saharan Africa, its impact on health and productivity is comparable to that of diseases with a global distribution. Since 1995, the average number of cases of HAT recorded per year has ranged between 37 977 (1998) and 6 750 (2011) and estimates of the global burden of HAT has ranged between 1.82 million disability adjusted life years (DALYs) in 2000 and 560 000 DALYs in 2010 [63]. Like many other neglected tropical diseases, the true burden of HAT is probably higher. Animal trypanosomiasis kills more than 1 million cattle each year [151] and the annual economic loss due to combined impact of human and animal trypanosomiases has been estimated at $2–4.5 billion.

There have been a number of recent reviews of HAT in general [32, 107, 180], and on particular matters such as chemotherapy [33], drug resistance [24], interactions between trypanosomes and tsetse [52, 126, 178], behaviour of tsetse [58, 167], epidemiology [55, 101] and vector control [164]. We therefore only summarise some of the important aspects of trypanosomiasis that are particularly relevant to the development and use of epidemiological models, focusing on the basic disease progression in humans and animals, the demographics of tsetse flies, trypanosome biology and efforts at controlling the infection.

1.1 Human African trypanosomiasis

The two forms of HAT have distinctive epidemiological, geographical, clinical and therapeutic characteristics as summarized below. Currently, the annual number of recorded cases is less than 10 000 per year, but about 70 million people are estimated to be at risk over an area of 1.5 million km^2 [152].

1.1.1 Gambian HAT

More than 95% of all cases of HAT are caused by *T. b. gambiense* transmitted by the *Palpalis*-group species of tsetse, particularly subspecies of *G. fuscipes* and *G. palpalis*. This group of tsetse, commonly called 'riverine tsetse', infest relatively humid habitats fringing the rivers, lake shores and wetlands of West and Central Africa.

The disease progresses over several years from the initial symptoms of fever, headaches and lymphadenopathy (known as Stage I disease) through neuro-psychiatric disorders (known as Stage II disease) and sleep disturbance (hence the common name of sleeping sickness) and in most cases death.

In contrast to most other important vectors (such as mosquitoes, blackflies, sandflies), both sexes of tsetse rely exclusively on blood for all their nutritional needs. Tsetse become infected after feeding on an infected host. The trypanosomes undergo a complex process of maturation in the fly and after a period of about 20–40 days the infective forms appear in the salivary glands of the fly and thereafter it remains potentially infective to any humans it bites. Flies vary in their susceptibility to initial infection with *T. brucei*. Most flies are inherently resistant to infection [179], and even those that are not resistant are most susceptible during their first blood meal. Unsurprisingly, the proportion of infectious tsetse is generally less than 1%. Gambian HAT is generally regarded as an anthroponosis with the parasite being transmitted between humans and tsetse only.

1.1.2 Rhodesian HAT

The remaining (5%) cases of HAT are caused by *T. b. rhodesiense* transmitted by the *Morsitans*-group of tsetse, especially subspecies of *G. morsitans* and *G. pallidipes* found in

the savannah woodlands of east and southern Africa. The transmission cycle for Rhodesian HAT is broadly similar to that of Gambian HAT except that Rhodesian HAT is a zoonosis with wild and domestic ungulates (e.g. warthog, bushbuck, buffalo, cattle) acting as important reservoir hosts. Indeed, many of the foci for Rhodesian HAT are wilderness areas where wild hosts and tsetse are abundant. Rhodesian HAT is a more acute disease than the Gambian form with the late stage neuro-psychiatric disorders occurring within weeks and death in months.

1.2 Animal African trypanosomiasis

The focus of this review is HAT but the disease is often co-endemic with animal trypanosomiasis. Accordingly national and global strategies to control these diseases are closely linked, and consideration of the animal disease provides insights into the epidemiology of HAT. The transmission cycle of AAT is broadly similar to HAT except that the hosts are livestock and wild ungulates. As with Rhodesian HAT, wild hosts can serve as a reservoir of disease for livestock especially in areas where livestock are close to wild hosts, for example, farming areas in Kenya and Tanzania adjacent to the Serengeti, Ngorongoro and Masai Mara National Parks. The causative agents of animal trypanosomiasis have less complex and generally faster rates of development in the fly than the subspecies of *T. brucei*; tsetse biting hosts infected with *T. vivax* and *T. congolense* become infective within around 10 and 20 days, respectively, and the probability that a mature infection results following feeding on an infected host is higher [126]. Tsetse are also more susceptible to infection from *T. vivax* throughout their life since the 'teneral effect', in which newly-emerged flies are more susceptible to infection than older ones, is unique to *T. brucei*. The upshot of these differences is that in areas where HAT and AAT are co-endemic, the prevalence of *T. vivax* and *T. congolense* in tsetse populations is higher (typically 1–5%) than that for *T. brucei* (about 0.1%).

1.3 Tsetse fly bionomics

1.3.1 Births and deaths

Tsetse have an unusual form of reproduction, termed adenotrophic viviparity, in which the larva develops within the female. From the age of about six days, adult females produce a single egg which matures in the uterus for about 7–12 days, the duration being dependent on temperature [70]. A single mature third-stage larva is deposited by the female on loose soil and it burrows into the ground and pupates. The time to deposition for subsequent larvae is shorter than for the first offspring, and the time between offspring decreases with increasing temperature. A mature adult fly emerges 20–40 days after deposition, and this pupal duration also decreases with increasing temperature [73, 129, 130]. This resultant low rate of reproduction is only sustainable because tsetse are relatively long lived. Ignoring deaths of larvae and pupae, adult female tsetse flies must live at least 25 days to ensure that they each produce two adult progeny. Such a low reproductive rate means that tsetse populations can only persist if the mean adult daily female mortality is less than 3.5% [69] which provides a crude target figure for control measures. Additionally, there can be substantial mortality in the pupal stage, due to predation [146], parasitism [71, 86] and extremes of temperature, the latter being important in setting the absolute limits to the distribution of tsetse flies and consequently HAT transmission.

While many models of vector-borne diseases assume a constant death rate, laboratory [41, 95, 96] and field [78] evidence indicates significant changes in tsetse mortality with age. In one field study female mortality was about 10% per day in newly emerged flies, fell to about 2% by age 10 days, increasing slowly thereafter. The pattern was similar for males but mortality increased much more rapidly with age. The changes relate to low fat levels and poorly developed flight musculature in newly-emerged flies, resulting in the double difficulty of needing to find and feed on a host rapidly but with a limited flight capacity [66]. Accordingly, many young tsetse flies either die of starvation, or by attempting feeding off high-risk hosts such as humans [66]. Those that do feed successfully build up energy reserves and flight muscles, and subsequent mortality declines. Increased mortality in older flies is associated with increased wing wear, resulting in diminished flight capacity. Adult mortality

also increases with temperature, and may be up to six times as high in the hot part of the year as in the cool part [74, 84].

1.3.2 Abundance and distribution

Tsetse populations are able to persist at remarkably low densities. Reliably estimating absolute densities of tsetse for sparse populations is difficult, but it seems likely that they can survive at densities of 1 tsetse/km^2 or less [60, 175], while the maximum density seems to be in the order of 10 000 tsetse/km^2 [84, 132, 173]. Traps used to sample tsetse are relatively inefficient; a single trap probably catches between 0.1% and 2% of the population per day [20]. The combination of tsetse persisting at low densities and inefficient sampling devices means that trypanosomiasis may be detected in the apparent absence of tsetse. This phenomenon is sometimes cited as evidence for mechanical transmission of trypanosomes by other biting flies such as horseflies and stable flies. However, it is more likely that in sub-Saharan Africa, low densities of tsetse are transmitting trypanosomes [101].

Tsetse are highly mobile, moving up to 1 km per day [72]. Savannah tsetse in relatively homogeneous woodland [68] or riverine tsetse in extensive wetlands [140] can be modelled adequately by assuming diffusive movement of tsetse through the habitat. For the more typical habitats of riverine tsetse however, flies are confined to the vegetation fringing rivers and lakes and hence displacement is largely along river margins and lake shores. The important consequence of the high mobility of tsetse is that populations of tsetse are seldom isolated and hence migration of tsetse into and out of a HAT focus is the norm.

1.3.3 Feeding interval

Males and females are obligate blood-feeders obtaining meals at 2–5 day intervals, as gauged from mark-recapture studies [59, 89, 90, 140, 145] or through analysis of wild-caught tsetse [80, 100, 133, 134]. The blood meal provides all of the fly's requirements for energy, water and growth, including production of larvae. This contrasts with most other vectors (e.g. mosquitoes, blackfly, sandfly) where only the female feeds on blood, and both sexes obtain some of their nutritional needs from feeding on plant sugars. Hence for tsetse there is an imperative to find and feed on a host regularly to avoid starvation.

The defensive behaviour of hosts and predatory insects (e.g. Asylidae and Bembicidae) in the host vicinity also pose a risk to feeding tsetse. Models of the costs and benefits of feeding have been used to analyse how tsetse balance the risk of starvation against feeding-related mortality. One analysis suggested that tsetse have an extended non-feeding phase of 3–4 days followed by a high feeding rate thereafter, it being assumed that tsetse can locate and feed on hosts efficiently [135]. In contrast, a second analysis suggested that tsetse do not display a marked change in feeding behaviour but rather become more responsive as their nutritional reserves decline [83]. Consequently, the probability of feeding on a host is modulated by the fly's reserves: newly-emerged tsetse and those that have not fed for several days are more likely to feed than mature flies or those that have fed recently [163, 170]. The balance between risk of starvation and feeding-related mortality probably varies with size of the fly and habitat. Smaller flies are less mobile and hence less efficient at locating hosts. Host location is also hampered by dense vegetation such as occurs in riverine habitats. As a consequence, a risk-averse feeding strategy is less marked in smaller tsetse (e.g. males, smaller species of tsetse) and riverine species [172].

1.3.4 Host selection

Tsetse use a combination of olfactory and visual cues to locate their hosts [58, 167]. Clausen *et al.* [38] provide summary results from analyses of 29 245 tsetse collected from 63 separate studies and covering 11 species of tsetse. In general, savannah tsetse feed on Suidae and Bovidae, particularly warthog and buffalo in wilderness areas and cattle where they are present. Experimental analysis of the attraction and feeding of savannah tsetse on various potential hosts demonstrated that a host's mass and its inherent rate of defensive behaviour determines its importance in the diet of tsetse [77, 161, 171]. In part, the avoidance of feeding on humans by *Morsitans*-group tsetse is modulated by hunger. Hungry flies are more likely to feed on humans. Humans are rarely bitten by savannah tsetse; odours and visual stimuli

produced by humans are repellent and those tsetse that do bite humans tend to be young and/or in an advanced stage of starvation [67, 162, 170].

Riverine tsetse have a broader range of hosts which can include primates, Suidae, Bovidae and reptiles, particularly the Nile monitor lizard [38]. Human odours and visual stimuli do not appear to be repellent to riverine tsetse [125, 137]. As a consequence, humans can form an important part of the diet. For instance, pooled analysis of blood meals from three species of riverine tsetse showed that 8% (454/5544) were from primates compared to only 1% (88/8660) for pooled data from four savannah species of tsetse [38]. The proportion of reptiles in the diet of some species of riverine tsetse is important since species of trypanosome pathogenic to humans and livestock cannot persist in reptiles [122]. Analysis of blood meals from *G. f. fuscipes* have shown that the proportion of meals from reptiles can be greater than 90% in tsetse caught from the shore of Lake Victoria where monitor lizards are abundant and about 40% elsewhere [38].

Studies of tsetse (*G. pallidipes*) feeding on groups of cattle suggest that most (over 90%) meals are taken from a single host (in one feed) [166] but analyses of the sources of blood meals suggest that mixed meals (from multiple feeds in one gonotrophic cycle) are not rare. For instance, a study in Mali found that that 30% ($n = 76$) of *G. tachinoides* and 17% of *G. p. gambiensis* ($n = 203$) contained blood from both humans and cattle [88]. Such mixed meals may arise from feeding on cattle and humans on successive days. The presence of blood from different hosts in a fly suggests that individual tsetse do not necessarily feed repeatedly on the same host species despite experimental evidence that *G. tachinoides* might 'learn' to feed preferentially on particular species [31].

Experimental studies of the behavioural responses of tsetse to hosts, and the marked preponderance or absence of potential host species in the diet of tsetse populations suggests that tsetse are selecting particular host species. However, we are aware of only one study that has simultaneously quantified the source of blood meals and the density of potential hosts simultaneously (the 'forage ratio' in mosquito literature): in the Serengeti National Park, Auty *et al.* used a combination of polymerase chain reaction (PCR)-based methods to identify sources of blood meals in tsetse and game-count transects to quantify densities of hosts [17]. Their results confirmed that tsetse preferentially select warthog and buffalo which are also important hosts for *T. b. rhodesiense*.

There is some evidence that selection of an individual host is modulated by its infection status. Studies in Kenya showed that feeding rates were higher on cattle infected with *T. vivax* and *T. congolense* [26, 27, 28, 114]. The higher rates may be due to infected animals attracting more tsetse and/or higher proportions of attracted tsetse feeding successfully; cattle infected with trypanosomes may display lower rates of defensive behaviour for instance. Alternatively, these animals may be more likely to be infected because they are more attractive to flies.

1.4 Trypanosome biology

1.4.1 Dynamics of trypanosomes in humans and animal hosts

The latent period between initial inoculation of *T. brucei* and a mammalian host becoming infectious is estimated to be about 7–14 days [15]. A systematic review of observed durations of subsequent infection for *T. b. gambiense* suggests that the mean ranges between several months and years, and is strongly right-skewed with some cases persisting for many years without morbidity or death [36, 92]. Analysis of 298 cases of Gambian HAT from northern Uganda suggests mean durations of 17 months for Stage I and 16 months for Stage II [37]. Severe illness and/or hospitalisation during Stage II may effectively remove the human host from the population of hosts by preventing contact with tsetse flies, in which case the mean duration of infectiousness would be about 17 months.

Recent studies of HAT patients in Côte d'Ivoire suggest that trypanotolerance, known to occur in wild hosts and some breeds of cattle, may also occur in humans [91]. Rather than the classical progression through Stage I, Stage II and death, some patients who showed clear parasitological and/or serological indications of infection with *T. b. gambiense* never developed neurological symptoms and ultimately appeared to self-cure, despite never receiving treatment. These infections were long-lasting (5–15 years) and hence this phenomenon could provide an important source of *T. b. gambiense*-infected individuals for onward transmission.

Duration of infection with *T. b. rhodesiense* in humans is much shorter, being of the order of about 6 months, with the distinction between first and second stages of disease less clear [7]. *T. brucei* infections in wild hosts and some livestock species and breeds may persist for longer periods [182] without severe adverse effects on animal mortality or morbidity [118]. Wild animal hosts which maintain chronic infections however have a lower parasitaemia [15, 113] and hence may be less infectious to tsetse [112].

Infections in cattle tend to result in an acute phase that occurs within weeks of infection that coincides with the first peak of parasitaemia followed by a chronic phase with a variably cryptic parasitaemia that can last for months to years [120]. Duration, magnitude and frequency of parasitaemia depends on breed of host, species and strain of trypanosome and the size of the inoculum.

Relatively few studies have experimentally inoculated and followed trypanosome infections in wildlife species for more than 60 days. However, the data available suggests that compared to cattle counterparts, parasitaemia is lower, its onset is later, and the observed pathology is less significant [51, 61, 149].

Following infection with *T. b. rhodesiense* via tsetse bite, parasites were detectable in warthog blood very sporadically for up to 5 to 25 days post-infection [15]. Infections persisting for several months have been measured in eland, impala, Thomson's gazelle and reedbuck [15, 40]. However, results from these studies must be treated with caution since the animals were often inoculated rather than infected by the bite of a tsetse fly, and animals kept in captivity may respond differently to those in the wild.

The trypanosomes pathogenic to humans and livestock evade the host's immune system by a process of antigenic variation in which the variant specific glycoprotein (VSG) coating the cell changes during the course of an infection [25]. Consequently, no vaccine against HAT has been developed and the prospects of one being developed are poor. A second consequence of antigenic variation is that the parasitaemia varies markedly and unpredictably with time [117] which may affect the likelihood of a susceptible tsetse being infected as it feeds.

1.4.2 Transmission of trypanosomes between hosts and vectors

The probability of a fly being infected depends not only on the levels of parasitaemia in the host but also the age, nutritional condition, sex and species of the fly itself.

The "teneral effect". Newly emerged unfed tsetse ("teneral" files) that are typically less than 3 days old are much more susceptible to infection with subspecies of *T. brucei* at their first blood meal than older flies [64]. Indeed, many models of HAT assume that infection can only occur in the first meal and thereafter flies are refractory ([141] and references therein). The "teneral effect" appears to be modulated by the nutritional status of a fly as evidenced by laboratory studies in which older refractory flies became susceptible to infection if they were starved [1]. The epidemiological significance of this effect of starvation is uncertain however. Flies that are in advanced stages of starvation are also at a greater risk of mortality, and older flies that become infected will need to survive for a further 20 days or more before they are themselves infectious.

Effect of species, sex and strain. Susceptibility of tsetse to infection is low according to laboratory studies of *G. pallidipes* and *G. m. centralis* feeding on cattle infected with *T. b. brucei*. One experiment, using a Tanzanian strain of *T. b. brucei*, showed that 3.7% of male and 1.8% of female *G. pallidipes* developed a mature (salivary gland) infection compared to 26.6% and 10.2% of *G. m. centralis*. In a second experiment using a Nigerian strain of *T. b. brucei*, none of the *G. pallidipes* developed a mature infection whereas 13.3% of male *G. m. centralis* and 5.6% of females did [115]. Studies of different strains of *T. b. rhodesiense* have shown that mean duration between initial uptake of trypanosomes and a mature infection varied between 18 and 23 days, and even within strains variation was high with a standard error between 2 and 8 days [42]. The probability of a mature infection developing in a fly appears to be correlated with slower rates of maturation [42] and reduced pathogenicity [181]. Similar inter-strain differences and generally low rates of maturation (0-10%) [136] are also seen with *T. b. gambiense*. As with experimental analyses of trypanosomes in mammalian

hosts, laboratory-based studies of trypanosomes with tsetse should be treated with caution because dynamics in wild strains may be different.

1.5   Control of African trypanosomiasis

The management of animal and human trypanosomiasis through various combinations of chemotherapies and vector control has been reviewed multiple times [32, 105, 107, 180] and hence we only summarize the important points.

1.5.1   Gambian HAT

Gambian HAT is generally assumed to infect humans only so control of Gambian has largely relied on the detection and treatment of cases. Starting in the 1920s and continuing through to the late 1950s, large scale campaigns of active case detection and treatment were conducted by the colonial authorities in the French and Belgian territories of West Africa (e.g. present day Burkina Faso, Cameroon and the Democratic Republic of Congo (DRC)). Following the strategy developed by Jamot in the 1920s in Cameron, mobile teams screened millions of people [157] for HAT.

Programmes of mass treatment with pentamidine were introduced as an early form of prophylactic chemotherapy, from the mid 1940s onwards with millions of people along the Congo river being regularly treated during the 1950s. These tactics reduced the annual number of recorded cases from over 50 000 per year in the 1930s to less than 10 000 per year by the early 1960s [153].

Efforts against Gambian HAT reduced in the immediate post-colonial period of the 1960s. The relatively low number of cases made HAT less important for newly independent countries with more pressing demands on their health services. Over the next 30 years, decline in the capacity of health services, socio-economic disturbances and war in many countries most at risk of HAT (e.g. Angola, DRC, Sudan, South Sudan, Uganda) contributed to further decline in global efforts against Gambian HAT. Consequently, the global number of cases reported annually steadily increased to a 1998 peak of 37 385. A revival of the global effort against HAT, led by the World Health Organization (WHO) and strongly supported by donations of chemotherapeutic drugs and diagnostics, has helped disease endemic nations to reduce the annual number of cases to the same levels as those reported in the early 1960s. The achievements of the past 20 years have been realized almost exclusively through active case detection and treatment. Screening of the population is based on the use of the Card Agglutination Test for Trypanosomiasis (CATT) followed by staging of positive cases through examination of the cerebrospinal fluid (CSF) which involves a lumbar puncture. Currently, the drugs used to treat Gambian HAT are pentamidine for Stage I and nifurtimox-eflornithine combination therapy (NECT) for Stage II. New drugs and diagnostics are in development. These include rapid diagnostic tests based on immunological and molecular methods [45, 111] and drugs such as fexinidazole and benzoxaboroles [183]. While vector control has not been an important part of efforts against Gambian sleeping sickness, the recent development of cost-effective methods to control riverine tsetse suggests that tsetse control will form an important part of efforts to eliminate Gambian HAT in the future [156].

1.5.2   Rhodesian HAT

Rhodesian HAT is a zoonosis so it cannot be controlled solely through detection and treatment of human cases, which are usually considered a spill over from a far larger number of chronic and less pathogenic cases occurring in populations of reservoir hosts. Treatment of humans cases is with either suramin for Stage I disease or melarsoprol for Stage II disease.

Most Rhodesian HAT foci are associated with wilderness areas where wild animals such as warthog, bushbuck and buffalo are the natural hosts of *T. b. rhodesiense* and various species of savannah tsetse are the vector. The difficulty of eliminating trypanosomes from wild hosts means that vector control is the only control option available. Currently, tsetse control methods used in wilderness areas include aerial application of non-persistent insecticides [98] or use of artificial baits to lure and kill tsetse [173, 49, 184]. Savannah tsetse are highly responsive to host odours and insecticide-treated targets baited with a blend of artificial host odours and deployed at densities of 4 targets/km^2 can eliminate populations of tsetse [174].

In SE Uganda, *T. b. rhodesiense* is transmitted by a species of riverine tsetse (*G. fuscipes fuscipes*) and cattle rather than wild hosts are the reservoir host. In this particular setting therefore, mass treatment of cattle with trypanocide and insecticide is a highly cost-effective option for control [5, 79, 165].

1.5.3 Animal African trypanosomiasis

In contrast to HAT, cheap, effective and safe prophylactic drugs exist for animal African trypanosomiasis as well as curative ones. In addition to being cheap (about $1 per dose), the drugs are easily administered through a single intra-muscular injection and are widely available. As a consequence, chemotherapy is the mainstay of efforts against animal trypanosomiasis with an estimated 35 million doses of trypanocide being administered each year. This approach has become particularly important following the decline in government-supported provision of veterinary services. However, chemotherapy is not without its problems. In particular, AAT cannot be eliminated without close to full coverage of the host population [79], which is particularly problematic where livestock mix with wild hosts, and drug resistance is increasing [34]. In addition, the productivity of livestock maintained in a tsetse-infested area, through regular treatment with trypanocide, is reduced compared to livestock kept in tsetse free areas [151]. Tsetse control also plays an important role in the control of AAT. In areas where densities of cattle are relatively high (greater than 10 animals/km^2), the use of insecticide-treated cattle is particularly cost-effective since the formulations effective against tsetse can also control tick-borne diseases of livestock [53]. Livestock are however not evenly distributed and in areas where their densities are low then other methods (insecticide-treated targets, aerial spraying, ground spraying) are used.

The mobility of savannah tsetse (up to 1 km/day) means that vector control must generally be applied at a scale (over 500 km^2) that cannot be achieved by individual livestock keepers [72, 164]. In the colonial period, government-supported tsetse control departments implemented large-scale control operations over areas of up to 10,000 km^2 each year [4] but the capacity to conduct operations on this scale of operation has declined since the 1960s. Consequently, sustainable and large-scale vector control operations are currently rare and identifying mechanisms where livestock keepers can implement tsetse control on a large scale without government or donor support is proving elusive.

1.5.4 Drug and insecticide resistance

A continuing worry with any drug- or insecticide-based intervention is that resistance may arise and undermine the control measures. Complacency is dangerous, but there are good grounds for believing insecticide resistance is likely to be less of a problem in controlling HAT than for many other diseases (malaria being the obvious co-endemic example). Tsetse are highly sensitive to insecticides compared to other insects, so the belief is that substantial increases in insecticide resistance (IR) levels would have to occur before they became operationally significant. Tsetse flies can respond to selection pressures for resistance, but since they are relatively long lived, with long generation times and low fecundity; they cannot respond as rapidly as short generation time and highly fecund species such as *anopheline* mosquitoes. Insecticide use for *T. b. gambiense* control is also highly focussed: the main tsetse vectors are highly mobile riverine species and control is focused on individual, relatively small, historically-stable HAT foci. These control measures will generate relative low selection pressures within the large, mobile contiguous populations of these species. Vector control mainly uses deltamethrin (a pyrethroid) but the exophilic lifestyle of the riverine tsetse species mean they rarely, if at all, enter huts where they could encounter pyrethroids used on bed nets or as residual sprays on wall. Also, unlike mosquitoes, tsetse demography makes them unlikely to encounter insecticides used in agriculture. There have been sporadic attempts to investigate resistance in the field [169] and by modelling [106] (notably predicting that it was unlikely to occur). The current belief in the tsetse community is therefore that IR is unlikely to be a significant operational threat in the foreseeable future.

Drug resistance in Gambian HAT is more plausible than IR in tsetse: the explicit aim of control efforts is to treat as many human infections as possible so that, given the belief that humans are the only significant non-tsetse host, this would imply very high selective pressure for resistance. Several drugs are used for Stage I infections and are all administered

under close clinical scrutiny. This means that factors such as poor patient compliance and under-dosing, believed to contribute to drug resistance in other pathogens, are less likely in treatment of Gambian HAT. Close clinical scrutiny also means that patients who do not respond adequately would be identified but, to date, no large scale drug-failures have been noted. Drug resistance, or at least reduced sensitivity, has been suspected to melarsoprol but only after around 50 years of use. The zoonotic nature of *T. b. rhodesiense* means that human treatment will leave a vast untreated reservoir of trypanosomes in other mammalian hosts so selection for resistance driven by human drug use is likely to be low. It is, of course, vital to ensure cattle are not treated with the same drug used to treat humans or this could drive widespread resistance. Finally, we note that people under treatment for HAT are usually very sick and likely to be confined to huts, or even treatment centres. They are therefore inaccessible to tsetse flies so that even if resistance does sporadically arise, it is unlikely to be transmitted back into the wider trypanosome population.

1.6   What has modelling ever done for HAT?

In contrast to the large number and widespread use of models to guide efforts against diseases as diverse as onchocerciasis [62], malaria [160], and influenza [124], models of HAT are few and their impact on practice and policy limited. Can models help in the war against trypanosomiasis? If so, why have they not been developed and used more widely?

We believe that there is a pressing need for models to answer the following questions to scientifically underpin he development of global and national strategies to eliminate HAT [2, 189]. What percentage of a human population needs to be screened and treated to eliminate a focus of Gambian HAT transmission? At what frequency should such a screen and treat program be repeated? What reduction in the density and longevity of tsetse flies is required to eliminate transmission of HAT? How long must interventions be applied to eliminate a focus? Why is HAT not more widespread, and will movement of reservoir hosts, tsetse or infected humans cause it to spread? How does HAT persist at the low levels of prevalence that have been measured in humans and tsetse flies? These questions require mechanistic models that capture the known behaviour of humans, tsetse and trypanosomes as well as matching the current epidemiological situation.

These questions were of less applied importance when national and global strategies were focussed on eradicating the vector and disease from countries or so-called 'fly belts' [94, 93]. This was achieved in a few cases (Botswana [98], Southeastern Zimbabwe [94], South Africa [50, 97], Northern Nigeria [43], Zanzibar [176]), but the general experience has been that attempts to completely and permanently eliminate tsetse and trypanosomiasis were unsuccessful. However, as we shall see, the few models of HAT that do exist suggest that elimination of HAT will not require killing the last fly or finding and treating the last case. Rather, reducing the mean infectious period of humans through case detection and treatment, and reducing the longevity and density of tsetse flies through vector control may eliminate transmission.

Following the longer history of malaria modelling, mathematical modelling of AAT began with Milligan and Baker (1988) [110] and HAT began with Rogers (1988) [141]. Since then, mulitple models of human and animal African trypanosomiasis have been built and analysed to investigate various aspects of trypanosome biology and epidemiology. Five of the most commonly considered aspects are: dynamics of infection in multiple mammalian host species, variations in tsetse fly susceptibility over its life span, stages of disease progression in mammalian hosts, spatial heterogeneity in transmission and tsetse population dynamics. Many models and analysis have then compared the effectiveness of the two widely used control interventions: treatment of infection humans and tsetse fly control; while recent models have also considered novel interventions such as targeting infection in tsetse flies.

We first outline the history of HAT modelling, including the malaria models that formed the foundations of the first (and most subsequent) HAT models. We then review the five features of HAT biology outlined above, describing the models and modelling approaches used and some of their key analysis and conclusions. We also derive and simulate extended models that combine some assumptions of published models to determine the implications of these assumptions. Finally, we summarize the progress made in modelling the effects of control interventions.

Table 1: Description of state variables of African trypanosomiases models in this review article. The subscript i represents hosts of different types and should be not confused with the state variables, i_{hi} and i_v, which represent proportions of infectious hosts or vectors.

Variable	Description
S_{hi}	Number of susceptible hosts of type i (who can become infected when bitten by infectious tsetse flies).
E_{hi}	Number of exposed hosts of type i (who are infected with trypanosomes but are not yet infectious to tsetse flies).
I_{hi}	Number of infectious hosts of type i.
R_{hi}	Number of removed hosts of type i (who are not infectious to tsetse flies and who may not get infected when bitten by infectious tsetse flies).
N_{hi}	Total number of hosts of type i. In some models, N_{hi} may be a parameter.
S_v	Number of susceptible tsetse flies.
E_v	Number of exposed tsetse flies.
G_v	Number of tsetse flies who are not infected but are not susceptible to infection.
I_v	Number of infectious tsetse flies.
N_v	Total number of tsetse flies. In some models, N_v may be a parameter.
s_{hi}	Proportion of susceptible hosts of type i (who can become infected when bitten by infectious tsetse flies). $s_{hi} = S_{hi}/N_{hi}$.
e_{hi}	Proportion of exposed hosts of type i (who are infected with trypanosomes but are not yet infectious to tsetse flies. $e_{hi} = E_{hi}/N_{hi}$.
i_{hi}	Proportion of infectious hosts of type i. $i_{hi} = I_{hi}/N_{hi}$.
r_{hi}	Proportion of removed hosts of type i (who are not infectious to tsetse flies and who may not get infected when bitten by infectious tsetse flies). $r_{hi} = R_{hi}/N_{hi}$.
s_v	Proportion of susceptible tsetse flies. $s_v = S_v/N_v$.
e_v	Proportion of exposed tsetse flies. $e_v = E_v/N_v$.
g_v	Proportion of tsetse flies who are not infected and are not susceptible to infection. $g_v = G_v/N_v$.
i_v	Proportion of infectious tsetse flies. $i_v = I_v/N_v$.

Most of the analysis of HAT models and the effects of interventions has been on the derivation of threshold conditions for persistence and general statements on the necessary conditions to eliminate HAT transmission. These models have substantially improved our understanding of HAT epidemiology, transmission and control but as described in the Outlook, §6, many features of HAT biology remain open to modelling. Additionally, given the current global call for HAT elimination [187], there is a need for properly validated models that can provide quantitative predictions of the impact and cost-effectiveness of control interventions in reducing transmission, and provide estimates on the time to potential elimination of control strategies.

2   Notation

Previous models used a variety of symbols for the same state variables and parameters. Here we adopt a standardised notation for all equations and figures to remain consistent and allow comparison across different models. The notation for state variables is described in Table 1, and for the parameters in Tables 2 and 3. We use upper case Latin letters to denote state variables or parameters representing numbers of animals; lower case Latin letters to denote state variables representing proportions of animals or dimensionless parameters; and lower case Greek letters to denote parameters representing rates.

The corresponding notation for the state variables and parameters used in previous modelling studies described in this review is shown in Tables 5 and 6 respectively.

Table 2: Description and dimension of parameters of African trypanosomiases models in this review article. In some cases where parameter values are the same for different types of hosts, the subscript i is dropped. For specialised models with other additional parameters, these parameters are described separately.

Parameter	Description
n	Number of different types of hosts that tsetse flies bite. These hosts may or may not be susceptible to trypanosomiases. Dimensionless
μ_{hi}	Per capita death rate of hosts of type i for $1 \le i \le n$. Dimension: Time^{-1}.
μ_v	Per capita death rate of tsetse flies. Dimension: Time^{-1}.
B_{hi}	Total birth rate of hosts of type i for $1 \le i \le n$. Dimension: Animals $\times$ Time^{-1}.
B_v	Total birth rate of tsetse flies. Dimension: Animals $\times$ Time^{-1}.
α	Biting rate of tsetse flies on all hosts. Dimension: Time^{-1}.
f_i	Proportion of bites of tsetse flies on hosts of type i for $1 \le i \le n$ given equal availability of all hosts. f_i measures the biting preference of tsetse flies on hosts of type i. $\sum_{i=1}^{n} f_i = 1$. Dimensionless.
δ_{hi}	Per capita disease-induced death rate of hosts of type i for $1 \le i \le n$. Dimension: Time^{-1}.
σ_{hi}	Per capita rate of progression of a host of type i for $1 \le i \le n$ from the exposed (latent) stage to the infectious stage. Dimension: Time^{-1}.
σ_v	Per capita rate of progression of tsetse flies from the exposed (latent) stage to the infectious stage (assuming an exponential distribution for the latency period). Dimension: Time^{-1}.
T_{hi}	Fixed duration of the intrinsic incubation period of host i. Dimension: Time.
T_v	Fixed duration of the extrinsic incubation period. Dimension: Time.
p_{hiv}	Probability of transmission of infection from an infectious tsetse fly to a susceptible host of type i (for $1 \le i \le n$) per bite. Dimensionless.
p_{vhi}	Probability of transmission of infection from an infectious host of type i (for $1 \le i \le n$) to a susceptible tsetse fly per bite. Dimensionless.
φ_{hi}	Per capita recovery rate for hosts of type i (for $1 \le i \le n$) from the infectious state to the recovered state. $1/\varphi_{hi}$ is the average duration of the infectious period. Dimension: Time^{-1}.
γ_{hi}	Per capita rate of loss of immunity for hosts of type i (for $1 \le i \le n$). $1/\gamma_{hi}$ is the average duration of the immune period. Dimension: Time^{-1}.

Table 3: Description of derived parameters of human African trypanosomiases models in this review article.

Parameter	Description
N_{hi}:	Stable population size of hosts of type i in the absence of disease when the per capita host birth rate is equal to the host death rate. $N_{hi} = B_{hi}/\mu_{hi}$. However, in some models, N_{hi} may be a state variable. Dimension: Animals.
N_v:	Stable tsetse fly population size when the per capita fly birth rate is equal to the fly mortality rate. $N_v = B_v/\mu_v$. However, in some models, N_v may be a state variable. Dimension: Animals.
λ_{hi}	Force of infection on hosts of type i. Dimension: Time^{-1}.
λ_v	Force of infection on tsetse flies. Dimension: Time^{-1}.
α_i	Biting rate of tsetse flies on hosts of type i for $1 \le i \le n$. $\alpha_i = \alpha f_i$. Dimension: Time^{-1}.
m_i	Ratio of number of hosts of type i to tsetse flies. $m_i = N_{hi}/N_v$. Dimensionless.

Table 4: State variables representing numbers of hosts or flies in previous models of HAT. The subscript i denotes the type of host. Unused state variables are left blank.

This review	S_{hi}	E_{hi}	I_{hi}	R_{hi}	N_{hi}	S_v	E_v	G_v	I_v	N_v
Artzrouni & Gouteux (1996) [9] [*]	H_s	H_i	H_a	H_r		V_s	V_i		V_a	
Funk et al. (2013) [56] [♯]			I_a		N_a		C_v[†]	G_v[†]	I_v	N_v

[*] Model only has human hosts, i denotes 'incubating' not host type

[♯] a denotes host type where $1 \leq a \leq n$, instead of using i

[†] These are only used for an extension to the model

Table 5: State variables representing proportions of hosts or flies in previous models of HAT. The subscript i denotes the type of host. Unused state variables are left blank.

This review	s_{hi}	e_{hi}	i_{hi}	r_{hi}	s_v	e_v	g_v	i_v
Aron and May (1982) [8]			x			z		y
Baker et al. (1990) [19]			y					$\hat{y}$
Milligan and Baker (1988) [110]	x	h	y	z[*]	$\hat{t}$	$\hat{h}$	$\hat{x}$	$\hat{y}$
Rogers (1988) [141]		w_i	x_i	z_i		f		y

[*] Cattle were assumed to be immune due to chemoprophylaxis. Wild animals had no immune class.

Table 6: Parameters in previous models of HAT. The subscript i denotes the type of host. Unused parameters are left blank. We use the birth rate parameters B_v and B_{hi} to model a constant birth and emergence rate of tsetse and hosts; however the models considered in this table do not explicitly use these parameters and assume that the birth rate is equal to the product of the mortality rate and the constant population size.

This review	μ_{hi}	μ_v	α	f_i	δ_{hi}	σ_{hi}	σ_v	T_{hi}	T_v	p_{hiv}	p_{vhi}	φ_{hi}	γ_{hi}	m_i
Aron and May (1982) [8]		μ	a						τ	b		r		m
Artzrouni and Gouteux (1996) [9][*]	m_h	m_v	τ_1[**]		r_2	q_h	q_v			τ_3	τ_2	r_1		
Baker et al. (1990) [19]		b	β				[§]			f	1^b	μ		V^{-1}
Funk et al. (2013) [56]	μ_a	μ_v	τ	f_a			α_v[‡]			b_a	b_v	γ_a		
Milligan and Baker (1988) [110]	μ	b	β	p, q	α			d	τ	f_1	$f_{2,3}$	r[♯]	γ	v
Rogers (1988) [141][†]		u	a_i[**]		i_i				T	b_i	c	r_i	v_i	m_i

[*] These parameters are scaled by bite rate^{-1} so that time is measured in 3 day periods rather than 1 day.

[**] This is actually αf_1 i.e. the human biting rate

[♯] Cattle move from the infectious class to the recovered class while wild animals return from the infectious class to the susceptible class.

[†] Rogers does not explicitly provide explicit parameter descriptions for T_{hi} but uses a circumflex to denote the value of state variables T_v or T_{hi} days in the past.

[‡] This are only used for an extension to the model

[§] Baker et al. do not explicitly model exposed flies but simply use a probability, P of the survival of infected flies to become infectious.

[♭] Baker et al. assume that the transmission probability from infectious hosts to teneral vectors of Rickettsia-like-organism infected flies is 100% and no other flies can get infected.

3 Models of African trypanosomiasis

3.1 History of trypanosomiasis modelling

Mathematical epidemiology of malaria has a rich history, beginning with Ronald Ross's dynamical model in the early twentieth century and George Macdonald's application of this model to epidemiological and entomological data in the mid-twentieth century [103, 104, 147, 148]. A series of models based on this analysis, commonly known as the Ross-Macdonald model, have formed the basis of much of the mathematical modelling of vector-borne diseases to date [138, 155]. In a 1982 review of malaria modelling, Aron and May [8] presented multiple versions of the Ross-Macdonald model, beginning with a description and analysis of a system of ordinary differential equations (ODEs) of the proportion of infected humans and mosquitoes and their interactions, assuming that the total population size of humans and mosquitoes was fixed. Although Aron and May's review focusses on malaria, we summarise it here because it is a valuable description of the Ross-Macdonald approach that has formed the basis of most HAT models to date. Figure 1 shows a schematic of the dynamics of the corresponding Ross-Macdonald model based on the number of susceptible and infectious hosts and vectors and the system of equations is given in (3.1).
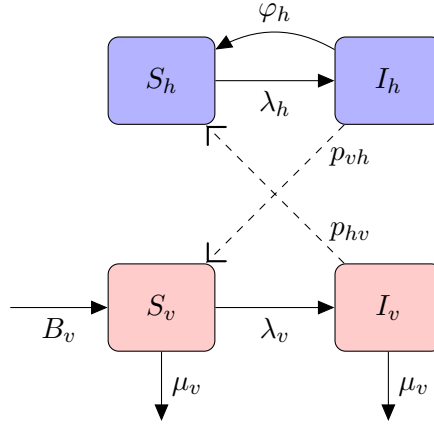

Figure 1: Compartmental diagram of the standard Ross-Macdonald model showing the number of hosts and vectors and transitions between compartments. Susceptible hosts (S_h) become infected from the bites of infected vectors (I_v) before returning to the susceptible state at a constant per capita rate. Susceptible vectors (S_v) emerge at a constant rate, B; become infected when they bite infected humans and remain infected for life. All vectors face a constant per capita mortality rate, μ_v. Solid lines show movement of individuals from one class to another, dashed lines show the paths of infection.

$$
\text{Hosts} \quad
\begin{aligned}
\frac{\mathrm{d}S_h}{\mathrm{d}t} &= \varphi_h I_h - \lambda_h S_h \\
\frac{\mathrm{d}I_h}{\mathrm{d}t} &= \lambda_h S_h - \varphi_h I_h
\end{aligned}
$$

$$ (3.1) $$

$$
\text{Vectors} \quad
\begin{aligned}
\frac{\mathrm{d}S_v}{\mathrm{d}t} &= B_v - \lambda_v S_v - \mu_v S_v \\
\frac{\mathrm{d}I_v}{\mathrm{d}t} &= \lambda_v S_v - \mu_v I_v
\end{aligned}
$$

where the constant total population of hosts is $N_h = S_h + I_h$; the force of infection on hosts, λ_h, is:

$$ \lambda_h = \frac{\alpha p_{hv} I_v}{N_h} $$

and the force of infection on vectors, λ_v, is:

$$\lambda_v = \frac{\alpha p_{vh} I_h}{N_h}.$$

The total vector population remains at a constant size $N_v = S_v + I_v$ if $B_v = N_v \mu_v$.

A simplified two-dimensional system of equations for the proportion of infected humans and vectors is shown in (3.2); this is based on the fact that host and vector population sizes remain constant so eliminating the need for two variables . We note here that Aron and May assumed that the probability of transmission of infection per bite of a susceptible vector on an infected human was one, $p_{vh} = 1$, and did not explicitly include a parameter for this probability. This probability was added to subsequent versions of the Ross-Macdonald model, starting from Anderson and May [6]; it is often labelled as c, but we retain the label p_{vh} for consistency of notation.

$$
\begin{aligned}
\text{Hosts} \qquad \frac{\mathrm{d}i_h}{\mathrm{d}t} &= m\alpha p_{hv} i_v (1 - i_h) - \varphi_h i_h \\[2mm]
\text{Vectors} \qquad \frac{\mathrm{d}i_v}{\mathrm{d}t} &= \alpha p_{vh} i_h (1 - i_v) - \mu_v i_v
\end{aligned}
\tag{3.2}
$$

One important simplifying assumption of this Ross-Macdonald model was that it ignored the latent period between infection with the parasite and becoming infectious and able to transmit the parasite. In humans, this latent period is small compared to the average life span so can be ignored. However in mosquitoes, this period is almost as long as the average life span so most infected mosquitoes die before becoming infectious. Aron and May described a system of delay differential equations (DDEs) that included this latent period in mosquitoes. A schematic of the dynamics of the corresponding model based on the number of susceptible and infectious hosts, and susceptible, exposed and infectious vectors is shown in Figure 2 and the system of equations is given in (3.3).
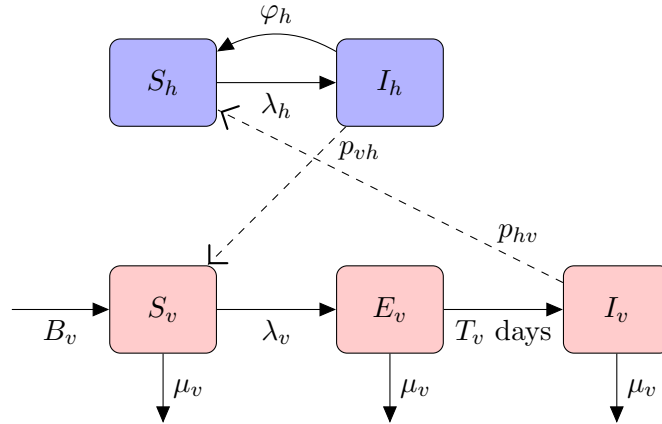

Figure 2: Compartmental diagram of the delay-differential equation Ross-Macdonald model showing the number of hosts and vectors. Susceptible hosts become infected from the bites of infected vectors before returning to the susceptible state at a constant per capita rate. Susceptible vectors emerge at a constant rate; become exposed to malaria when they bite infected humans; become infected after a fixed time, T_v, and remain infected for life. All vectors face a constant per capita mortality rate.

$$
\text{Hosts} \quad
\begin{aligned}
\frac{\mathrm{d}S_h(t)}{\mathrm{d}t} &= \varphi_h I_h(t) - \lambda_h(t) S_h(t) \\
\frac{\mathrm{d}I_h(t)}{\mathrm{d}t} &= \lambda_h(t) S_h(t) - \varphi_h I_h(t)
\end{aligned}
$$

$$(3.3)$$

$$
\text{Vectors} \quad
\begin{aligned}
\frac{\mathrm{d}S_v(t)}{\mathrm{d}t} &= B_v - \lambda_v(t) S_v(t) - \mu_v S_v(t) \\
\frac{\mathrm{d}E_v(t)}{\mathrm{d}t} &= \lambda_v(t) S_v(t) - \lambda_v(t - T_v) S_v(t - T_v) e^{-\mu_v T_v} - \mu_v E_v(t) \\
\frac{\mathrm{d}I_v(t)}{\mathrm{d}t} &= \lambda_v(t - T_v) S_v(t - T_v) e^{-\mu_v T_v} - \mu_v I_v(t)
\end{aligned}
$$

where the total (constant) population of hosts is $N_h = S_h(t) + I_h(t)$; the total (constant) population of vectors is $N_v = S_v(t) + E_v(t) + I_v(t)$ (assuming $B_v = N_v \mu_v$); the force of infection on hosts, $\lambda_h(t)$, is:

$$
\lambda_h(t) = \frac{\alpha p_{hv} I_v(t)}{N_h}
$$

and the force of infection on vectors, $\lambda_v(t)$, is:

$$
\lambda_v(t) = \frac{\alpha p_{vh} I_h(t)}{N_h}
$$

Similar to the reduction from (3.1) to (3.2), Aron and May reduced the five-dimensional system (3.3) to a three-dimensional DDE model for the proportion of infectious humans and exposed and infectious vectors, as shown in (3.4).

$$
\text{Hosts} \quad \frac{\mathrm{d}i_h(t)}{\mathrm{d}t} = m\alpha p_{hv} i_v(t)(1 - i_h(t)) - \varphi_h i_h(t)
$$

$$
\text{Vectors} \quad
\begin{aligned}
\frac{\mathrm{d}e_v(t)}{\mathrm{d}t} &= \alpha p_{vh} i_h(t)(1 - e_v(t) - i_v(t)) \\
&\quad - \alpha p_{vh} i_h(t - T_v)(1 - e_v(t - T_v) - i_v(t - T_v)) e^{-\mu_v T_v} - \mu_v e_v(t) \\
\frac{\mathrm{d}i_v(t)}{\mathrm{d}t} &= \alpha p_{vh} i_h(t - T_v)(1 - e_v(t - T_v) - i_v(t - T_v)) e^{-\mu_v T_v} - \mu_v i_v(t)
\end{aligned}
$$

$$(3.4)$$

The basic reproductive number, R_0, is defined in mathematical epidemiology as the expected number of secondary infectious caused by one infectious individual in a fully susceptible population through the duration of the infectious period. R_0 provides a threshold condition for epidemic models: when $R_0 < 1$, the trivial disease-free equilibrium point is asymptotically stable and introduced cases do not lead to epidemics or the establishment of the disease in the population. When $R_0 > 1$, the disease-free equilibrium point is unstable and introduced cases can lead to epidemics or to a new endemic steady state. Hence calculation of R_0 is a critical step in understanding persistence or eradication of infection.

For this model, Aron and May define the basic reproductive number as the number of new infections in humans from one infected human through a generation of infected vectors,

as shown in (3.5).

$$R_0 = \begin{pmatrix} \text{Number of} \\ \text{vector bites} \\ \text{per human} \\ \text{per time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{transmission} \\ \text{from human} \\ \text{to vector} \end{pmatrix} \begin{pmatrix} \text{Duration of} \\ \text{infection} \\ \text{in humans} \end{pmatrix}$$

$$\times \ (\text{Probability of vector surviving latent period})$$

$$\times \begin{pmatrix} \text{Number of} \\ \text{bites on humans} \\ \text{per vector} \\ \text{per time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{transmission} \\ \text{from vector} \\ \text{to human} \end{pmatrix} \begin{pmatrix} \text{Expected} \\ \text{infectious} \\ \text{life span} \\ \text{of vectors} \end{pmatrix}$$

$$= (m\alpha)\,(p_{vh}) \left(\frac{1}{\varphi_h} \right) \left(e^{-\mu_v T_v} \right) (\alpha)(p_{hv}) \left(\frac{1}{\mu_v} \right)$$

$$= \frac{m\alpha^2 p_{hv} p_{vh} e^{-\mu_v T_v}}{\varphi_h \mu_v} \tag{3.5}$$

This relatively simple equation (3.5) demonstrates that it is more effective to reduce the vector biting rate, α, and the adult vector death rate, μ_v, than to reduce the vector density, m. As such this provided justification to the Global Malaria Elimination Program for its main control strategy of targeting adult vectors through indoor residual spraying.

The basic reproductive number has also been defined for vector-borne diseases as the number of new infections from one generation to the next (the geometric mean of the number of new infections from humans to vectors and from vectors to humans), following the next generation operator approach of Diekmann *et al.* [46]. This definition of the basic reproductive ratio is the square-root of that defined from humans through vectors and back to humans. Although the two definitions provide different numerical values for the basic reproductive number, they provide the same threshold condition at $R_0 = 1$.

Rogers [141] expanded this DDE model to produce some of the first models of African trypanosomiases: for *T. vivax, T. congolense* and *T. brucei*. His main extensions to the malaria model were: to add a second species of vertebrate hosts; to add "exposed" and "immune" states to the vertebrate hosts; and to only allow a certain proportion of susceptible vectors to become infected when they bite infectious hosts (p_{hv} which was included in subsequent versions of the Ross-Macdonald model). We show a schematic of the corresponding model for the number of hosts and vectors in each class in Figure 3.

Rogers only presented the three differential equations for the proportions of infectious hosts (of both types) and vectors. He described the intrinsic incubation period, both as a fixed duration, and as exponentially distributed with a constant rate of becoming infectious (labelled as $1/i$), but only showed the equations for the fixed duration. We show the full system of equations (for the proportion of hosts and vectors), assuming a fixed duration for the intrinsic incubation period in (3.6),

$$\text{Hosts (i=\{1,2\})} \quad \begin{aligned} \frac{\mathrm{d}s_{hi}}{\mathrm{d}t} &= \gamma_{hi} r_{hi}(t) - \lambda_{hi}(t) s_{hi}(t) \\ \frac{\mathrm{d}i_{hi}}{\mathrm{d}t} &= \lambda_{hi}(t - T_{hi}) s_{hi}(t - T_{hi}) - \varphi_{hi} i_{hi}(t) \\ \frac{\mathrm{d}r_{hi}}{\mathrm{d}t} &= \varphi_{hi} i_{hi}(t) - \gamma_{hi} r_{hi}(t) \end{aligned}$$

$$\text{Vectors} \quad \begin{aligned} \frac{\mathrm{d}e_v}{\mathrm{d}t} &= \lambda_v(t)(1 - e_v(t) - i_v(t)) - \mu_v e_v(t) \\ & \quad - \lambda_v(t - T_v)(1 - e_v(t - T_v) - i_v(t - T_v)) e^{-\mu_v T_v} \\ \frac{\mathrm{d}i_v}{\mathrm{d}t} &= \lambda_v(t - T_v)(1 - e_v(t - T_v) - i_v(t - T_v)) e^{-\mu_v T_v} - \mu_v i_v(t) \end{aligned}$$
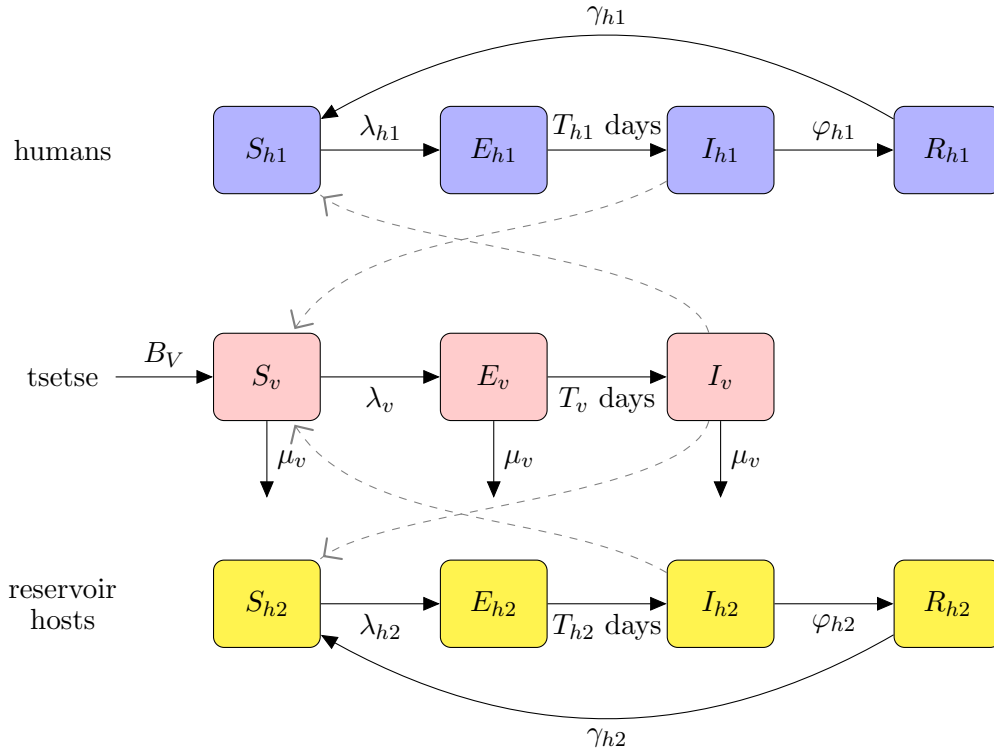
$$\tag{3.6}$$

Figure 3: Compartmental diagram of the delay-differential equation model of HAT dynamics in Rogers (1988) [141] showing the number of humans, reservoir hosts and vectors. Susceptible humans, S_{h1}, become latent with infection from the bites of infectious vectors. After a fixed period of time, latent humans, E_{h1} become infectious to tsetse flies. Infectious humans, I_{h1} recover at a constant rate to become immune. Recovered humans, R_{h1}, lose their immunity to infection at a constant rate (γ_{hi}) and return to the susceptible class. Birth and mortality in humans is ignored. Reservoir hosts are assumed to have similar dynamics to those for humans. Susceptible vectors, S_v emerge at a constant rate; become exposed to HAT when they bite either infectious humans or reservoir hosts; become infectious after a fixed time, T_v, and remain infectious for life. All vectors face a constant per capita mortality rate. The total population sizes of humans, reservoir hosts and vectors are assumed to be constant.

Here, the force of infection on hosts of humans ($i = 1$) and reservoir hosts ($i = 2$) is:

$$\lambda_{hi}(t) = m_i \alpha_i p_{hiv} i_v(t)$$

and the force of infection on tsetse flies is:

$$\lambda_v(t) = \sum_{i=1}^{2} \alpha_i p_{vhi} i_{hi}(t)$$

The equations for the proportion of exposed hosts are redundant because exposed hosts encounter no mortality and simply introduce a delay from the susceptible to the infectious class; and the proportion of exposed hosts is $e_{hi}(t) = 1 - s_{hi}(t) - i_{hi}(t) - r_{hi}(t)$ for $i = 1, 2$. The proportion of susceptible vectors is $s_v(t) = 1 - e_v(t) - i_v(t)$.

Rogers described the endemic equilibrium point of this system of equations as the implicit solution to a system of three simultaneous equations, and showed a phase portrait for a prescribed set of parameter values of the solutions approaching a globally asymptotically stable equilibrium point.

Due to the complications in deriving the basic reproductive number for HAT as derived for malaria in (3.5) with two different types of hosts, Rogers defined the basic reproductive number as the expected number of secondary infections in tsetse flies from one infected tsetse fly, through a generation of infection in humans and reservoir hosts, assuming fully susceptible host and vector populations.

Although this definition may provide a different expression than that defined from the next generation operator approach, both expressions provide the same threshold condition for the loss of stability of the disease-free equilibrium point and the existence of a positive asymptotically stable endemic equilibrium point:

$$R_0 = \frac{e^{-\mu_v T_v}}{\mu_v} \left(\frac{m_1 \alpha_1^2 p_{h1v} p_{vh1}}{\varphi_{h1}} + \frac{m_2 \alpha_2^2 p_{h2v} p_{vh2}}{\varphi_{h2}} \right) \tag{3.7}$$

again pointing to the importance of the vector adult mortality rate and biting rate. Rogers [141] derived parameter values to model,what he called a typical village in West Africa, except for the transmission probability parameters, p_{vhi} and p_{hiv}, which he estimated from East African field data and laboratory experiments. Details of the parameter values and their subsequent revisions are provided in §3.2.

From this parameterisation, Rogers derived equilibrium prevalence values for hosts and vectors and modelled the change in equilibrium infection rates as a function of tsetse mortality. Similar to previous analysis for malaria, Rogers' sensitivity analysis showed that equilibrium prevalence of trypanosomiasis was most sensitive to the duration of the feeding cycle of tsetse flies (which relates to the biting rate on humans, α_1, and reservoir hosts, α_2), followed by the tsetse mortality rate, μ_v. However, his calculated values for equilibrium prevalence in humans (and reservoir hosts) were much higher than values measured in the field. This has remained an issue for most models of HAT.

Rogers used a separate model to include the teneral effect in flies for *T. brucei* (where tsetse flies are only susceptible for the first few days of their life). The details of this model and subsequent extensions and analysis by other authors is described in §3.4. Rogers also simulated seasonality in transmission by allowing the mortality rate of tsetse flies, μ_v to vary periodically, as described with subsequent extensions in §3.7.

Milligan and Baker [110] published their first model of animal trypanosomiases in the same year as Rogers' paper. They included enhanced vector susceptibility in teneral flies, multiple host types (cattle and wild animals) and disease-induced mortality in both hosts and vectors. They derived the basic reproductive number and modelled the effects of chemoprophylaxis on cattle. They showed that the effectiveness of chemoprophylaxis depends on the frequency of application and duration of protective efficacy and that the effectiveness of vector control is reduced by the immigration of flies.

3.2 Parameter values for trypanosomiasis models

Parameter values and their ranges are typically based on a combination of estimates obtained from field data and literature, expert opinion, and assumptions adopted from previous modelling exercises. Many of the model parameter values are reasonably well defined, such as

Table 7: Values for *T. b. gambiense* used in this paper and possible ranges of parameters (rate parameters have dimensions of days^{-1}). Many parameters depend on the temperature tsetse and humans are exposed to, and most values for these parameters assume a stable temperature of around 25°C.

Parameter	Value	Range	Source
μ_{h1}	4.4×10^{-5}		assumption
μ_{hi}	Varies		
μ_v	0.034	$0.014 - 0.047$	[74, 44]
α	0.33	$0.25 - 0.5$	[74, 44]
δ_{h1}	0.002	$0.0013 - 0.0029$	[37]
δ_{h2}	0		
σ_{hi}	0.083		[9]
σ_v	0.034	$0.025 - 0.034$	[9, 44]
p_{hiv}	0.62		[141]
p_{vhi}	0.065	$0.001 - 0.2$	[141, 44]
φ_{hi}	0.0019	$0.0012 - 0.0028$	[37]
γ_{hi}	0.02		[141]
m_i	Varies		

those related to tsetse longevity, and baseline values and ranges are shown in Table 7. Here, we highlight two key components that have either used a wide range of values based on differing underlying assumptions, or have been based on assumptions that have been proven erroneous by more recent estimates.

3.2.1 Tsetse susceptibility to trypanosomes

The probability of a fly becoming infected when feeding on a parasitaemic individual will depend on a variety of factors, and a fairly wide range of parameter values have been used in HAT models.

Most models have used the same assumption that only teneral flies can become infected with trypanosomes, but have differed in their assumptions about teneral duration and the infection risk associated with feeding during this period. Artzrouni and Gouteux [9] used a value of 0.1 and suggested a range of 0.05–0.14, and assumed that the teneral state lasted until the initial blood feeding. Rogers [141] used a value of 0.065 but assumed that the window of infectivity lasted only a day for *T. b. gambiense*. Milligan and Baker [110] included a teneral phase but used 0.05 as the probability for infection for both teneral flies and non-teneral flies, despite stating that this probability should be enhanced for the initial blood meal.

More recently a number of HAT models have foregone the modelling of an explicit teneral phase and simply used mean values for $\tilde{p}_{vhi}$. This could be interpreted as a constant:

$$\tilde{p}_{vhi} = p_{vhi} \frac{\mu_v}{\mu_v + \alpha}$$

which is mathematically equivalent at equilibrium if the tsetse suffer a constant mortality rate throughout their lifetime. However, it becomes a simplifying assumption when more realistic tsetse dynamics, seasonality or time-varying effects of vector control are included, since the proportion of teneral flies may change. Funk *et al.* [56] estimated a value of 0.18, applicable over the entire lifespan of tsetse, while Moore *et al* [116] used a value of 0.0355 based on Baylis [29]. Walshe *et al* [178] provided experimental data on the teneral phenomenon for *G. m. morsitans*: for the first blood meal about 55% of flies established trypanosomes in the midgut, but these higher levels of establishment may be an artefact of laboratory settings where susceptible tsetse lines are used to increase rates of infection to aid study of tsetse-trypanosome interactions.

3.2.2 Duration of the infectious period in hosts

Rogers [141] used values of between 50 (*T. brucei* infections) and 100 days (*T. congolense* and *T. vivax*) for the duration of the infectious period in hosts but admitted that these figures were "crude average, or intermediate, values from the wide ranges in Hoare's book" [87]. Subsequent reviews (at least of HAT epidemiology in Uganda although there may be less or more virulent strains elsewhere) have shown the duration to be on the order of 17 months, so a reasonable value for Gambian HAT is closer to 1000 days [36]. For *T. b. rhodesiense* most models have assumed an infectious duration between one and three months [44, 18], which is closer to the observed data.

3.3 Modelling multiple host species

The terminology regarding reservoirs has evolved over the past years, but has not reached a widely accepted convention. Haydon *et al.* [85] suggested that a "maintenance" host should be defined as a host type that can sustain transmission in the absence of transmission events from other host types. A "reservoir" would represent a species or community from which transmission events to a target population of interest (e.g. humans) occur, regardless of whether the reservoir species is negatively affected by the pathogen.

Whether the label of reservoir species should extend to those species that do contribute to transmission but are not essential for maintenance of the disease (incidental or liaison hosts) is a matter where opinions diverge. Ashford [16] excluded these species, leading to a concept of a set of species required to maintain transmission indefinitely. This is comparable to the concept as used by Nishiura *et al* [121] and Funk *et al* [56], who argue that the reservoir should include all maintenance hosts and a minimal set of non-maintenance hosts.

Reservoir and maintenance hosts can be described using three threshold quantities derived from a next-generation matrix (NGM) approach described by Diekmann, Heesterbeek and Roberts [47]: the basic reproduction number, R_0; the host-specific reproduction number, U; and the host-excluded reproduction number, Q [139]. A host species i can be considered a maintenance host if the host-specific contribution to R_0 is greater than unity, that is $U_i > 1$. A host or community of hosts can be considered a reservoir if in addition to $U_i > 1$, R_0 in the absence of transmission from this host species is less than one, that is $Q_i < 1$.

The extent to which humans and non-humans form maintenance or reservoir hosts for Gambian HAT remains a contentious issue. In several locations *T. b. gambiense* has been isolated from non-human animals [109, 123, 154]. One study in a focus in Cote d'Ivoire reported *T. brucei* in both humans and pigs, but suggested these consisted of different zymodemes (that is, different populations or strains) indicating that there may have been little genetic exchange between the two transmission cycles [92]. In the laboratory, infection of various non-human animals and subsequent infection of tsetse has been accomplished. For instance, infected pigs harbouring low levels of *T. b. gambiense* were able to infect *G. m. submorsitans*, but interestingly not laboratory colony specimens of *G. p. gambiensis* [186].

In spite of these observations, the commonly held belief is that gambiense HAT is mostly an anthroponosis, with only incidental transmission to and from non-humans. This is partly based on clinical field experiences where treatment of the human population succeeded in eliminating HAT from certain foci [188] and is one reason human screening and treatment remains the main tool employed against Gambian HAT.

A number of HAT modelling studies have suggested an opposite view: that the contribution of humans alone to R_0 would be below 1 and humans should therefore not be considered a maintenance host species [141, 44, 56]. In the model of Rogers [141], where one alternate host type is modelled and could be interpreted as a population of domestic pigs, this species would constitute a maintenance host species (although Rogers assumed a very short duration of the infectious period in humans and R_0 for humans could be greater than one with a longer duration). Multiple species are considered by Funk *et al.* [56], none of which by themselves are capable of maintaining transmission, rather a mix of multiple domestic or wild animals, potentially in combination with humans, are required. Resolving these issues will require further field studies, particularly longitudinal measurements of prevalence in non-humans potentially linked with genetic information on infecting trypanosomes.

Further modelling studies may also wish to keep the simplifying assumptions inherent to these models in mind. For instance, both Rogers and Funk assume a fixed proportion of

bites for host species, rather than a proportion based on preference and relative population sizes (e.g. Milligan and Baker [110]; Moore *et al.* [116]). Further, Rogers assumes mortality of the hosts to be negligible and omits this factor, while Funk *et al* present data based on a susceptible-infected model, omitting an incubating class for vectors (although they mention that inclusion of this state does not qualitatively change their outcomes).

The interplay between two host species (humans and animals) and the tsetse is crucial in understanding how HAT infection might be controlled and eliminated. It has been hypothesised that control methods such as culling animal populations in order to prevent cross-host infections (animal to tsetse to human), may result in the tsetse shifting their biting patterns to focus more on the human population, and potentially increase disease prevalence. Basic models of HAT, incorporating one host (human) population (e.g. [9, 10]) are attractive due to their simplicity but they run the risk of failing to capture realistic dynamics potentially caused by secondary host populations. In order to ensure that control methods will both produce the desired results and be effective, the interdependence of HAT and the effects of two or more host species must be carefully modelled.

A first (perhaps naïve) postulate is that any non-human blood-meals (from species such as lizards [12, 11]) are not able to transmit HAT. In this case, the Ross-Macdonald model has a slightly altered force of infection for hosts:

$$\lambda_h = \frac{\alpha p_{hv} I_v}{N_h + N_o} \tag{3.8}$$

where N_h is the population of humans and N_o is the number of other hosts scaled by the proportion of blood meals that are taken from them by tsetse. Whilst these non-human hosts do not explicitly play a role in the transmission cycle, their presence could (in large enough numbers) avert tsetse biting away from the human population and hence reduce disease prevalence (see Figure 4). Work by Hargrove *et al.* suggests that that if 80% or more of bites do not occur on humans then this is enough to reduce R_0 to less than 1 for Rhodesian HAT [79].
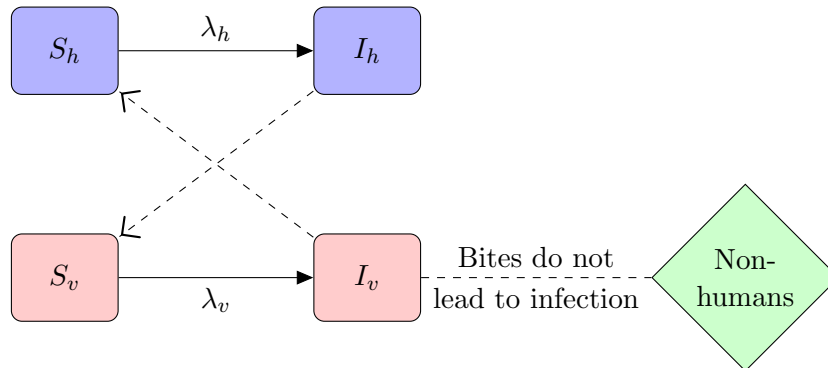

Figure 4: The simplest multi-host model with non-human hosts that do not contribute to onwards infection. These dead-end hosts do, however, reduce the tsetse biting rate upon humans and so effectively reduce forces of infection upon both hosts and vectors.

Another standard approach to multi-species modelling for HAT as taken by Rogers [141], Milligan and Baker [110] and many others is to partition the total host population into two categories, humans and (other) animals. Tsetse flies must select a single host from either category upon feeding and so the force of infection, both on the tsetse and to either host species, is dependent on this selection (see Figure 5).
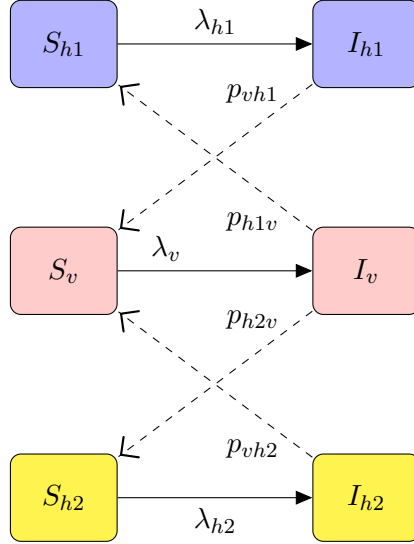
Figure 5: Interplay between the vectors and multiple host species. Here the vector selects host species i to feed on with probability f_i. Two host species are shown here but this could be easily extended for n host populations.

$$
\text{Hosts, } i = \{1, \ldots, n\} \qquad
\begin{aligned}
\frac{\mathrm{d}S_{hi}}{\mathrm{d}t} &= B_{hi} - \lambda_{hi} S_{hi} - \mu_{hi} S_{hi} \\
\frac{\mathrm{d}I_{hi}}{\mathrm{d}t} &= \lambda_{hi} S_{hi} - (\mu_{hi} + \delta_{hi}) I_{hi}
\end{aligned}
\tag{3.9}
$$

$$
\text{Vectors} \qquad
\begin{aligned}
\frac{\mathrm{d}S_v}{\mathrm{d}t} &= B_v - \lambda_v S_v - \mu_v S_v \\
\frac{\mathrm{d}I_v}{\mathrm{d}t} &= \lambda_v S_v - \mu_v I_v
\end{aligned}
$$

Note that each species has its own demographic and disease parameters, based upon average life expectancies, disease susceptibility and progression. The force of infection for hosts is given by:

$$
\lambda_{hi} = \frac{f_i \alpha p_{hi}}{N_{hi}} I_v \qquad \text{where } i = \{1, \ldots, n\}
\tag{3.10}
$$

where f_i is the proportion of blood-meals that a tsetse will take from host species i. The force of infection is calculated by considering the bite rate multiplied by the probability of selecting a host of type i from all hosts (f_i), multiplied by the probability of transmission from vector to a host i, times the probability of selecting a susceptible host from all hosts of type i and, finally, by the number of infectious vectors.

The force of infection for vectors is given by:

$$
\lambda_v = \sum_i \frac{f_i \alpha p_{vhi}}{N_{hi}} I_{hi} \qquad \text{where } i = \{1, \ldots, n\}
\tag{3.11}
$$

or (if $p_{vhi} = p_{vh}$ for all i):

$$
\lambda_v = p_{vh} \alpha \left(\frac{f_1 I_{h1}}{N_{h1}} + \cdots + \frac{f_n I_{hn}}{N_{hn}} \right)
\tag{3.12}
$$

Here the literature diverges into two alternate (but relatable) ways of dealing with host selection by tsetse.

The first uses a fixed host preference, f_i, where the proportion of bites taken upon species i remains constant, regardless of host population sizes. The force of infection for this fixed preference is given in (3.10). This formulation may prove most useful in terms of parameter

ascertainment as ingested blood-meals can be used to find the proportion of feeds from different host species. Sometimes the term αf_i is written as α_i; this can be considered the biting rate of tsetse upon host species i.

The second formulation takes the tsetse's innate host preference into account along with relative host species availability so that f_i and α_i are dependant upon state variables, specifically the numbers of each host species, and so are expected to change dynamically. In the case where there are just two host species the weighting of bites is given by the vector $s = (s_1, s_2)$ where:

$$\frac{s_i}{s_1} = \text{ratio of host preference from host } i \text{ to host 1 when population sizes are the same}$$

For example, when $s_1 = 1$ and $s_2 = 2$ there are twice as many bites on animals ($i = 2$) than humans ($i = 1$) (for equal population sizes). The biting preference weighting makes host species 2, s_2/s_1 times more preferable than species 1, and it is equivalent to increasing the secondary host population by a factor of s_2 then selecting one host out of the total.

This second formulation gives a variable biting preference for each host species, which is more suitable if host numbers fluctuate. For two host species we find:

$$f_i(N_1, N_2) = \frac{s_i N_{hi}}{s_1 N_{h1} + s_2 N_{h2}} \tag{3.13}$$

and, as before, this can be extended for n species:

$$f_i(N_1, \ldots, N_n) = \frac{s_i N_{hi}}{\sum_{j=1}^{n} s_j N_{hj}} \tag{3.14}$$

Conversely weighting s may be found if current population sizes and proportions of blood meals are known. For instance for two species, s_1 is generally fixed at 1 and so:

$$s_2 = \frac{N_{h1} f_2}{N_{h2}(1 - f_2)} \tag{3.15}$$

This type of host preference is used by Milligan and Baker in their cattle/wild animal model [110].

For fixed population sizes the two method are equivalent. However the advantage of the sliding preference over the fixed one becomes apparent when one or more of the host populations size change (through disease, migration, culling, etc.) — it is assumed that a tsetse's innate preference will not change, but host availability will alter feeding patterns. Likewise, if f_i is unknown in some region but the host population sizes are known, it may be reasonable to use the weighting of bites s (calculated from (3.15)) from a neighbouring area, utilising the known host ratios, and extrapolate to find f_i for the new area.

To explore the potential impact of some of these assumptions of host biting preference, we write a next generation matrix model (NGM) for the case of two host species and one vector, using two different forces of infection. These formulations of the model ignore the teneral phenomenon and use an averaged value for p_{vhi} (following Funk *et al* [56]). With a fixed biting preference, the force of infection on host species then is:

$$\begin{aligned}
\lambda_{h1} &= \alpha f_1 p_{h1v} \frac{I_v}{N_{h1}} \\
\lambda_{h2} &= \alpha f_2 p_{h2v} \frac{I_v}{N_{h2}}
\end{aligned} \tag{3.16}$$

where f_1 is the proportion of bites on host species 1, and we assume f_2 is equal to 1-f_1. With a biting preference that scales with host numbers, the force of infection becomes:

$$\begin{aligned}
\lambda_{h1} &= \alpha \frac{s_1 N_{h1}}{s_1 N_{h1} + s_2 N_{h2}} p_{h1v} \frac{I_v}{N_{h1}} \\
\lambda_{h2} &= \alpha \frac{s_2 N_{h2}}{s_1 N_{h1} + s_2 N_{h2}} p_{h2v} \frac{I_v}{N_{h2}}
\end{aligned} \tag{3.17}$$

Here, as before, s_i describes the relative propensity or aversion to feed on host species i when the host species are equally abundant.

Writing the Jacobian of the system of equations, isolating the infected compartments, and separating into matrices T for transmission events and Σ for rates at which individuals exist the infected stages, the NGM is then given by $K = -T\Sigma^{-1}$. For a system with one vector species and two hosts:

$$K = \begin{pmatrix} 0 & 0 & k_{13} \\ 0 & 0 & k_{23} \\ k_{31} & k_{32} & 0 \end{pmatrix} \tag{3.18}$$

The basic reproduction number, R_0, is the dominant eigenvalue of K, squared to reflect transmission from humans to vectors back to humans, $R_0 = k_{13}k_{31} + k_{23}k_{32}$, while the host-specific contributions to R_0, are then $U_i = k_{i3}k_{3i}$.

For the first type of (fixed) host preference these are given by:

$$U_1 = \frac{\alpha^2 p_{h1v} p_{vh1} S_v \sigma_{h1} \sigma_v f_1^2}{N_{h1}(\sigma_{h1} + \mu_{h1})(\gamma_{h1} + \mu_{h1})\mu_v(\sigma_v + \mu_v)} \tag{3.19}$$

$$U_2 = \frac{\alpha^2 p_{h2v} p_{vh2} S_v \sigma_{h2} \sigma_v f_2^2}{N_{h2}(\sigma_{h2} + \mu_{h2})(\gamma_{h2} + \mu_{h2})\mu_v(\sigma_v + \mu_v)} \tag{3.20}$$

and for the second type of (variable) host preference these are given by:

$$U_1 = \frac{\alpha^2 p_{h1v} p_{vh1} S_v \sigma_{h1} \sigma_v N_{h1} s_1^2}{(s_1 N_{h1} + s_2 N_{h2})^2 (\sigma_{h1} + \mu_{h1})(\gamma_{h1} + \mu_{h1})\mu_v(\sigma_v + \mu_v)} \tag{3.21}$$

$$U_2 = \frac{\alpha^2 p_{h2v} p_{vh2} S_v \sigma_{h2} \sigma_v N_{h2} s_2^2}{(s_1 N_{h1} + s_2 N_{h2})^2 (\sigma_{h2} + \mu_{h2})(\gamma_{h2} + \mu_{h2})\mu_v(\sigma_v + \mu_v)} \tag{3.22}$$

Fixing the population sizes of humans and tsetse, Figure 6 considers the impact of changes in biting preference and population size of host species 2 for the two formulations of biting preference (f - top row, s - bottom row). The columns show the effects on the total R_0 and the contributions of both hosts (U_1 and U_2). Figure 7 shows the impact of the background mortality rate of the second host type on R_0 for models based on s; for models based on fixed f, host mortality has limited impact.

The upper row of plots of Figure 6 was created assuming a fixed biting preference (force of infection as in (3.16)), while the lower row used the opportunistic or sliding biting preference (3.17). The plots graphically represent the numerical evaluation of R_0 (right-most plots) and the host-specific contributions to R_0, U_1 and U_2 for host types 1 (e.g. humans) and 2 (e.g. pigs), respectively, when varying the preference to bite host type 1 (f_1 and s_1) and the size of the second host type population, but keeping all other parameter values constant. The thick black line indicates where (the host-specific contribution to) R_0 is equal to one. If one assumes that only humans contribute to transmission, and non-human animals do not, then R_0 becomes equal to the host-specific contribution to R_0 of humans, U_1. The plots of U_1 highlight that it is theoretically feasible for transmission to occur without an animal reservoir, if the biting preference for humans is large enough (a point to the right of the black line). However, if we let the biting preference depend on relative population sizes (sliding or opportunistic host utilisation), U_1 depends on an interaction between the population size of species 2 and the the innate preference to bite humans, s_1, so that at higher densities of species 2, a level of anthropophily unknown to tsetse would be required for U_1 to be > 1. If an animal reservoir does exist, there is only a small part of the parameter space where R_0 is < 1 (the red area above the black line in the plots of R_0). Figure 7, which depicts the values of R_0 (assuming two host species contribute to transmission) when again varying the population size of the second host species and the innate preference for biting humans, highlights that the lifespan of the non-human host species also has an important influence on transmission: if this is short enough (e.g. 1 year, which may occur if pigs are being kept but slaughtered frequently), R_0 may be below 1 even with an animal reservoir, if sufficient animals are kept.
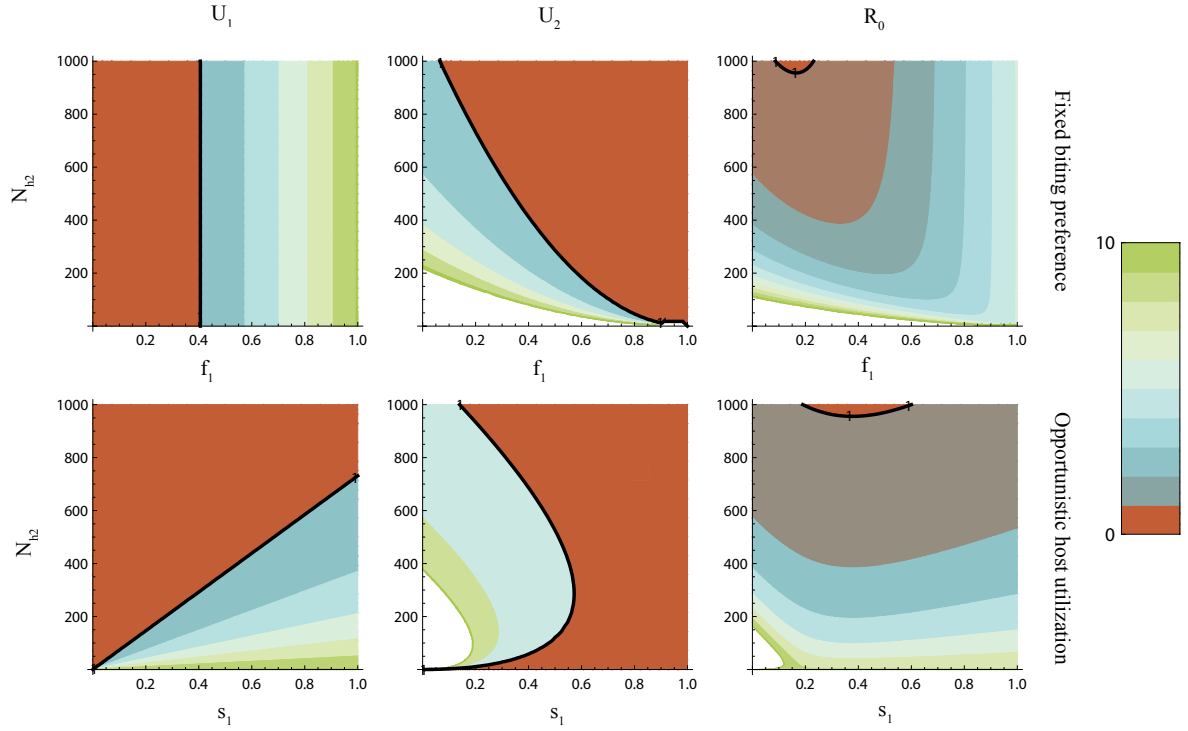
Figure 6: A comparison of implications on R_0 and the contribution of host types based on two approaches to modelling vector biting preferences (fixed or variable) for $N_{h1} = 500$ and $N_v = 2000$. The value of R_0 is indicated by contours, with the red colour corresponding to a value less than 1. The contribution of host types 1 and 2 to R_0 are indicated by U_1 and U_2, respectively. With the second assumption of variable biting, the presence of animals (e.g. pigs) that do not contribute to transmission (U_1) dilutes or acts as a protective screen: a greater number of an alternative host reduces R_0. If the second host type does contribute to transmission, a relatively large population size will be required for R_0 to remain below 1.
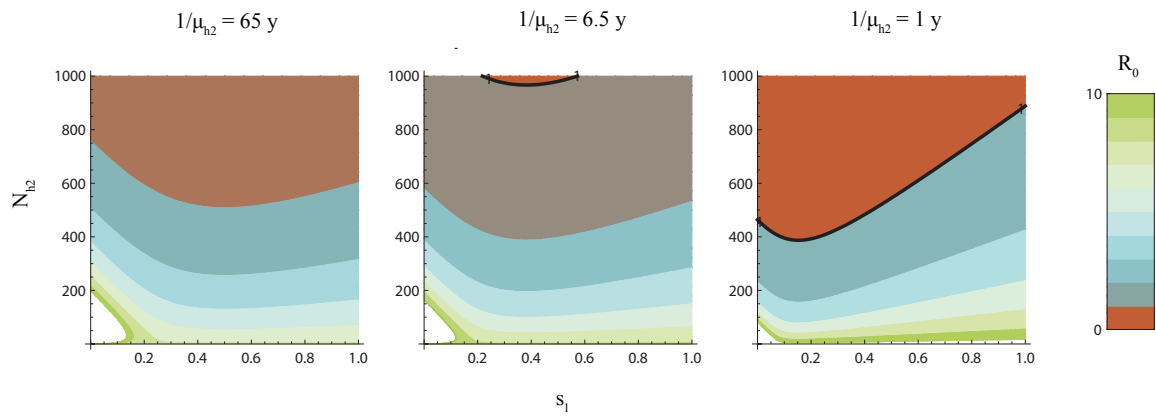
Figure 7: Contours of R_0 (red colour corresponding to $R_0 < 1$) illustrating the impact of the background mortality rate of the second host type in conjunction with population size (N_{h2}) and biting preference (where $s_1 = s_2$ represents a non-selective feeder whose choice depends merely on relative population sizes and values closer toward 0 representing an increasing aversion to biting humans). The shorter the lifespan of the second host, the lower the value of R_0. These results suggest that the keeping of peridomestic livestock such as pigs influences HAT transmission in several ways and depends on the proportion of humans to livestock and the rate at which livestock is slaughtered.

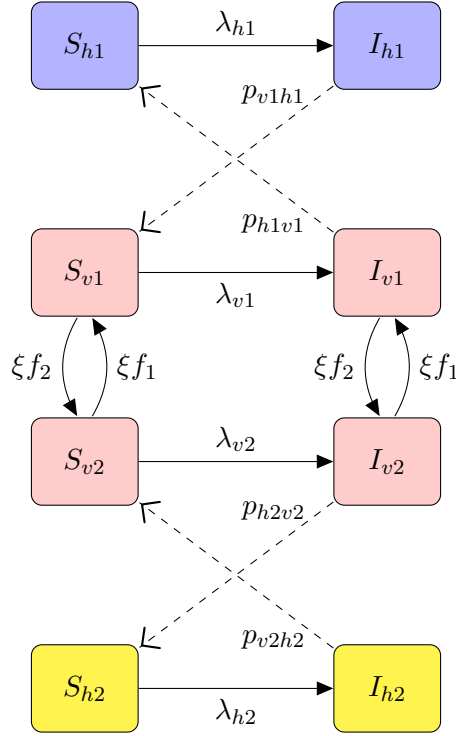### 3.3.1 Correlated bites on mammalian host species

Figure 8: Interplay between the vectors and multiple host species with correlated bites (in this case $n = 2$). Here there are n classes of vectors, one for each host species. Vectors of class vi feed exclusively upon host species i until switching class which happens at a rate ξ and independently of infection status.

Some studies [31] suggest tsetse may select their hosts with a preference for the species which provided the previous blood-meal. To incorporate this notion of correlated bites Funk *et al* [56] assumed that vectors will feed upon one species, say host species 1 for an average period of time ξ^{-1} and then switch to another host of species 2, chosen by vectors host preference given by f_2.

Vectors are partitioned by the species from which their last blood-meal came and teneral flies are assigned a class in proportion to the f_i's. This gives rise to n susceptible and n infected vector classes. Note that whilst hosts and vectors both have n susceptible and n infected classes, hosts are born into one species and do not switch (other than from susceptible to infected). Vectors on the other hand switch at a rate ξ between classes independently of infection status.

Equations for the vectors now become:

$$\frac{\mathrm{d}I_{vi}}{\mathrm{d}t} = \lambda_{vi}S_{vi} - \mu_v I_{vi} - \xi I_{vi} + \sum_j \xi I_{vj} f_j \tag{3.23}$$

The demographic parameter (μ_v) is independent of the last species bitten since mortality is independent of the source of the last blood-meal and here, as previously, the force of infection is given by:

$$\lambda_{vi} = \alpha p_{vhi} \frac{I_{hi}}{N_{hi}} \tag{3.24}$$

Host equations will now become:

$$\frac{\mathrm{d}I_{hi}}{\mathrm{d}t} = \lambda_{hi}S_{hi} - \mu_{hi}I_{hi} - \varphi_{hi}I_{hi} \tag{3.25}$$

where the force of infection is simply:

$$\lambda_{hi} = \alpha p_{hiv} \frac{I_{vi}}{N_{hi}} \tag{3.26}$$

with the force of infection only associated with the class of vector that will bite that particular host species.

It is contentious whether or not correlated bites happen in general and there is only minimal corroboration for this assertion. Consequently, Funk *et al.* [56] have the only known model to incorporate this feature.

3.4 Modelling vector competence

Vector competence is a broad term that encompasses how amenable a vector species is to parasite uptake, establishment, and development, typically denoted as a single parameter (p_{vhi} in our notation) in compartmental models. Vector competence represents a spectrum ranging from refractoriness to susceptibility and in reality is influenced by a wide range of immune and physical mechanisms within the vector. The outcomes differ not only between tsetse species and trypanosomiasis strains, but also between and within individual tsetse.

Typical assumptions in models have been that tsetse flies have increased susceptibility during their first blood meal and lower susceptibility during subsequent feeding; however some models have also included variations in susceptibility and mortality in flies due to the nutritional status of the fly and the presence of symbionts.

3.4.1 Teneral and age-dependent susceptibility

To capture teneral susceptibility, the Ross-Macdonald model (3.1) was adapted by adding another class of flies, G_v, that consists of non-teneral flies whose first blood-meal did not lead to infection and who consequently cannot become infected (or may only become infected at a lower probability). This allows for an alternative formulation in which a different compartmental model is used for the tsetse population (see Figure 9). This formulation and slight variations follow naturally from the biology and implementation discussed by several authors (including Milligan and Baker [110], Rogers [141], Artzrouni and Gouteux [11], Medlock *et al* [108] and Funk *et al* [56]).
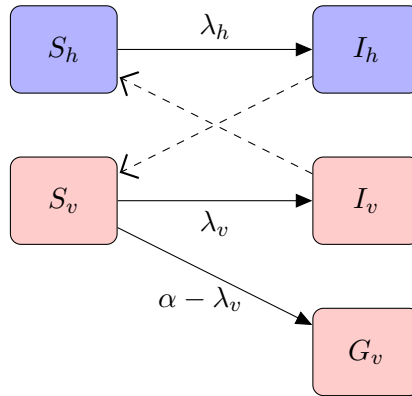

Figure 9: Schematic of model for teneral susceptibility. Here the G_v compartment represents flies that have fed at least once and were not infected on their fist feed (and are subsequently outside of the disease dynamics).

The new ODEs are:

$$\text{Hosts} \quad \begin{aligned} \frac{\mathrm{d}S_h}{\mathrm{d}t} &= B_h + \gamma_h I_h - \lambda_h S_h - \mu_h S_h \\ \frac{\mathrm{d}I_h}{\mathrm{d}t} &= -\gamma_h I_h + \lambda_h S_h - (\mu_h + \delta_h)I_h \end{aligned}$$

$$\text{Vectors} \quad \begin{aligned} \frac{\mathrm{d}S_v}{\mathrm{d}t} &= B_v - \lambda_v S_v - \mu_v S_v \\ \frac{\mathrm{d}I_v}{\mathrm{d}t} &= \lambda_v S_v - \mu_v I_v \\ \frac{\mathrm{d}G_v}{\mathrm{d}t} &= (\alpha - \lambda_v)S_v - \mu_v G_v \end{aligned} \tag{3.27}$$

where the force of infection, λ_i, remains the same as previously (i.e. (3.8) where there are no reservoir hosts). New refractory vectors (class G_v) arise from susceptible vectors biting (at rate α) whose first bite did not lead to infection (due to either biting a non-infected host or from failure of transmission). The refractoriness is assumed to be complete and life long and since biting is assumed to be frequency rather than density dependent, the bite rate is independent of the host(s) population(s). Many authors do not explicitly model the refractory, non-teneral class. Artzrouni and Gouteux [11] use an approximation method to compute the teneral population (S_v) by assuming the population is approximately at equilibrium and so:

$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = B_v - \alpha S_v - \mu_v S_v \approx 0 \tag{3.28}$$

which gives:

$$S_v^* = \frac{B_v}{(\mu_v + \alpha)} \tag{3.29}$$

Artzrouni and Gouteux note that $\alpha > \mu_v$ (significantly, $\alpha \approx 1/3$ days^{-1} whereas $\mu_v \approx 1/33$ days^{-1}) and so $S_v^* \approx \frac{B_v}{\alpha}$. It is this value S_v^* which is used throughout their work as an approximation of S_v.

Rogers [141] also uses this type of equilibrium argument to compute the teneral population and, again, eliminate the need for explicit modelling of refractory flies. However an additional requirement of susceptibility in the model is that un-fed flies must be less than t days old to be able to transmit infection at the next blood-meal. The number of flies less than t days old (given that bites and deaths are considered Poisson processes and hence are exponentially distributed) is given by:

$$\mathbb{P}(\text{un-fed fly} \leq t \text{ days old}) = \int_0^t (\mu_v + \alpha)e^{-(\mu_v+\alpha)x} \, \mathrm{d}x = 1 - e^{-(\mu_v+\alpha)t} \tag{3.30}$$

and so:

$$S_v^* = \frac{B_v}{\alpha + \mu_v}(1 - e^{-(\alpha+\mu_v)t}) \tag{3.31}$$

Using parameters given by Rogers [141], this extra requirement on age reduces the susceptible population by around 33% compared to the un-fed population total yielding about 8% of the tsetse population susceptible (rather than 11%). Arguably the stipulation that teneral flies must be less than t days old may represent not only the loss of susceptibility of these flies, but the expected mortality associated with newly emergent tsetse failing to take a blood-meal. Blood-feeding in tsetse is a necessity for survival, not only for reproduction as with the mosquito (although female mosquitoes also use blood for energy and survival), and newly emerged tsetse are more prone to starvation than tsetse who have fed at least once [99]. Models of this increased mortality are described in more detail below in §3.4.2.

Both Rogers [141] and Artzrouni and Gouteux [11] assume fixed vector population sizes so this removes the need to model the refractory class explicitly. Milligan and Baker [110] take another approach based upon a similar principle. In their model, tsetse either become infected and are considered exposed (E_v), upon the first blood-meal, or their susceptibility to HAT reduces by a factor, denoted here by ε, for subsequent blood-meals and so they move to a 'non-teneral' class (G_v) (see Figure 10) so the immunity to infection is not complete.
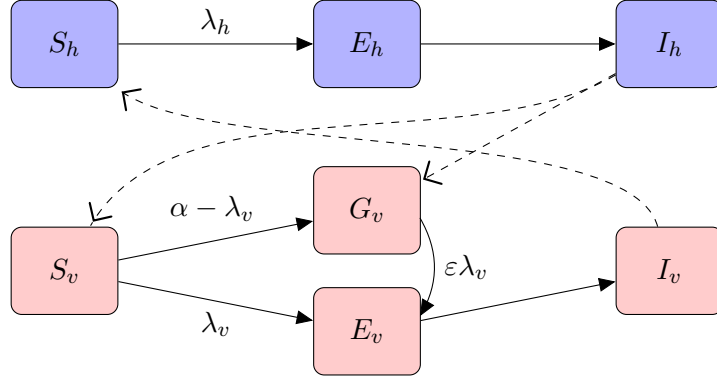
Figure 10: Transmission patterns including partial non-teneral immunity. Here then fed flies may still play a role in the transmission cycle, however they have a reduced force of infection (by ε) compared their unfed counterparts.

While under Rogers' formulation, the number of susceptible flies is less than the number of un-fed flies, the modelling of teneral flies described in Figure 10 has the opposite effect: the number of flies which may acquire infection upon biting is greater than the number of un-fed flies.

Refractoriness was also prominently featured in a study based on an NGM approach to obtain expression for the basic reproduction number [44], where in addition to the teneral phenomenon, they assumed that only a small fraction of teneral flies are susceptible to infection. This is different from a more intuitive interpretation of having a single low value of p_{vhi}, where all (teneral) flies have a small probability of becoming infected, although the distinction only matters when it is tied to genetics or to the harbouring of intra-cellular symbionts (see below). The NGMs they derived for *T. b. gambiense* and *T. b. rhodesiense* differed in their inclusion of livestock and wild animal host types, though both allowed for transmission by two vector species, *Glossina fuscipes fuscipes* and *G. pallidipes* or *G. morsitans*. A global sensitivity analysis revealed that the proportion of blood meals taken on humans was the parameter that most strongly influenced R_0 for *T. b. gambiense*, while for *T. b. rhodesiense* refractoriness to trypanosomes ranked highest. Surprisingly, tsetse survival was only of moderate importance, which deviates from the typical interpretation of vectorial capacity [57], where vector survival, together with the biting rate, are thought to affect transmission potential most strongly (as described above in §3.1). An interesting outcome, which potentially lends further support to the notion of an animal reservoir, was that over the range of their defined parameter space, R_0 for *T. b. gambiense* was below one, but above one for *T. b. rhodesiense*.

In their agent-based model, Muller *et al.* [119] explicitly included an age-dependent susceptibility that increased over the first three days of a fly's life but then decreased rapidly as a function of age. As is typically the case with agent-based models, the lack of an explicit algebraic formulation makes it difficult to interpret the effect of this assumption on their simulation results.

3.4.2 Effect of nutritional status

Blood is the only food source of tsetse flies, so without it, tsetse flies starve. Formulating starvation in an ODE model framework can be achieved by introducing an additional death rate, μ_{vT}, which affects all members of the tsetse population equally unless the population is further subdivided. Mathematically this does not change the equations, because this term may be considered to be included in μ_v, the 'natural' mortality of tsetse, μ_v (through a reparameterisation).

It is well documented that teneral flies must feed soon after emergence [74, 78, 99]. The size and nutritional reserves of teneral flies vary [74] and this seems likely to contribute to variation in not only mortality but also in the feeding behaviour of these flies. We can include

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faster teneral starvation by amending only the susceptible fly population:

$$\frac{\mathrm{d}S_v}{\mathrm{d}t} = B_v - \alpha S_v - \mu_v S_v - \boldsymbol{\mu_{vT}S_v} \tag{3.32}$$

whilst leaving the other equations as before. Here μ_{vT} is the additional starvation rate experienced by teneral flies only. 'Normal' starvation of all tsetse is included in the μ_v term.
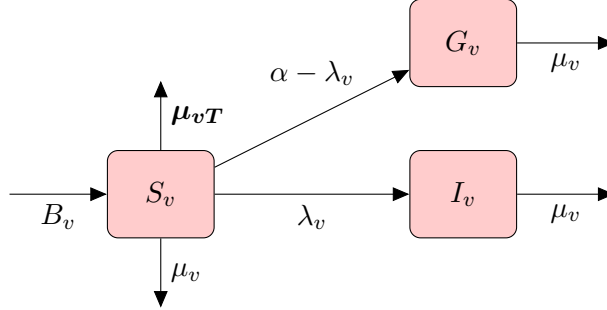

Figure 11: Compartmental diagram showing a possible implementation of teneral tsetse starvation. Here previously unfed tsetse experience an additional starvation pressure of μ_{vT} compared to their non-teneral counterparts.

If the births into the population, B_v, compensate for this extra teneral starvation (as would be expected for stable populations), there is no change to the number of either susceptible or 'immune' tsetse, consequently there is no change from teneral starvation to infection in either hosts or vectors.

Rogers' model [141] does not include faster starvation of teneral flies, but has a similar assumption by removing teneral flies older than t days old from the system. However, whilst not explicitly stated, these flies remain in the population, rather than dying. The formulation of this model calculates the number of surviving teneral tsetse, younger than t days using (3.30).

Using the given parameters of Rogers [141], the number of teneral flies is 66% less than that predicted when assuming that flies only lose their susceptibility through biting alone. This is since $t < 1/\mu_v$ and so:

$$1 - \exp(-(\alpha + \mu_v)t) < 1 - \exp(-(\frac{\alpha + \mu_v}{\alpha})t) \approx 0.67 \tag{3.33}$$

A visualisation of the type of reduction in teneral flies given by Rogers' model is given in Figure 12.
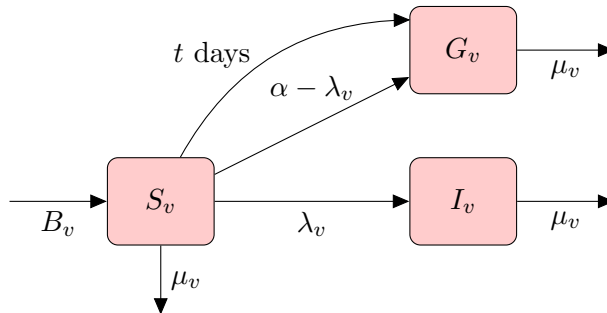

Figure 12: Compartmental diagram showing a possible implementation of teneral tsetse loss of susceptibility through ageing. Here susceptible tsetse are lost through biting at a rate α or through becoming older than t days.

Realistically the feeding frequency α would also be expected to be higher for newly emergent tsetse than non-teneral flies leading to a higher exit rate from the susceptible class into the 'immune' class. This would have a similar type of impact to Rogers' loss of susceptibility of teneral flies.

Modelling the increase in susceptibility due to starvation is difficult to capture in ODE models because of the assumption of a homogeneous fly population and exponentially distributed biting times. This would be relatively easy to include in an agent-based model that tracks individual flies, such as the one by Muller *et al.* [119] but they do not alter susceptibility by time since last feed.

3.4.3   Effects of symbionts

Tsetse flies are host to a number of intracellular symbionts: *Wigglesworthia glossinidius*, *Wolbachia pipientis*, and *Sodalis glossinidius*. Both *Wigglesworthia* and *Sodalis* are thought to be symbiotic by contributing B-complex vitamins that are lacking in the blood-only diet of the tsetse and longevity is reduced in flies lacking these symbionts. *Sodalis*, initially described as a *Rickettsia*-like organism, has been incriminated as having a role in refractoriness. In certain, but not all tsetse populations, the presence of *Sodalis* in flies was found to be correlated to their susceptibility to infection. One hypothesis for this is that *Sodalis*, particularly in teneral flies, can inhibit certain lectins within the midgut environment that normally disrupt trypanosomes, although this notion has fallen out of favour in recent years [**?**]. A model incorporating the role of *Rickettsia*-like organisms (*Sodalis glossinidius*) was developed by Baker *et al* [19] to explain periodic oscillations in human prevalence. They make the critical assumptions that *Sodalis*-infected tsetse flies enjoy a higher pupal survivorship; that only teneral *Sodalis*-harbouring flies are susceptible to infection with trypanosomes; and that trypanosome infection negatively affects tsetse fitness (reduced fecundity rather than pathogen-induced mortality). The change in the proportion of infected hosts (only one population is considered) is:

$$\frac{\mathrm{d}i_h}{\mathrm{d}t} = \left(\frac{\alpha_h^2 m_h p_{hv} \exp(-\mu_v T_v)}{\mu_v + \alpha_h} \right) \theta i_h(1 - i_h) - \varphi_h i_h. \tag{3.34}$$

This is a modification of the Ross-Macdonald model, where α_h is the biting rate on humans, m_h the number of tsetse per human, p_{hv} the probability of an infectious bite leading to infection, $\exp(-\mu_v T_v)$ the probability of a tsetse surviving the extrinsic incubation period, μ_v the rate of tsetse mortality, θ the proportion of flies harbouring *Sodalis*, φ_h the rate at which humans lose infection, and i_h the fraction of humans that are infected with HAT. The novel component of their model is a differential equation for the fraction of *Sodalis*-infected flies,

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = \frac{1}{\tau_g}\theta(1 - \theta)\frac{(k - gi_h)}{(1 - k + \theta(k - gi_h))} \tag{3.35}$$

where k is the fractional gain in pupal survival due to the symbiont and g the fractional loss in fecundity due to trypanosome infection, and τ_g the time between generations. The equilibrium solution of (3.35) leads to the interpretation that when *Sodalis* is not at fixation ($\theta \neq 1$) nor entirely absent ($\theta \neq 0$) in the population, the fraction of infected humans depends only on the proportional increase of larval survival due to *Sodalis* and the cost due to trypanosome infection,

$$i_h^* = \frac{k}{g} \tag{3.36}$$

and not directly through vector density, biting rate or adult mortality. Lack of *Sodalis* in this model thus functions as a form of tsetse immunity, and gives rise to oscillations and periodic (circa 20 year cycles) epidemics if the vectorial capacity is high enough. An increase in trypanosomiasis prevalence will serve to reduce the fraction of flies infected with *Sodalis* until prevalence reaches a low level and *Sodalis* will again increase, but very slowly due to the low reproductive rate of tsetse and the small fitness advantage associated with the symbiont. A strange conclusion that follows from this work is that vector control (barring elimination of the tsetse population) would not in the long run affect disease prevalence, because a lowered vectorial capacity will merely result in a higher proportion of *Sodalis*-infected flies. These results all hinge on the assumptions of the model, which may not hold for all field populations.

3.5 Modelling stages of disease progression in mammalian hosts

Under Rogers' formulation decreasing mammalian host immunity to infection is included, but host demography (births and deaths) is not. The various models in the literature are not consistent in how disease progression in mammalian hosts is modelled. For instance whilst Rogers' 'removed' class accounts for recovered individuals with immunity to disease, Artzrouni and Gouteux [10] use four host stages where the latter two correspond to first and second stages of the disease (asymptomatic and symptomatic respectively) and there is no immune effect (recovery is immediately into the susceptible class).

Interestingly, although these disease progression models are biologically very different, they are mathematically similar in formulation and the schematic shown for humans in Figure 3 is unchanged as Artzrouni and Gouteux assume that humans with secondary stage disease are not available for blood-feeding of tsetse and are therefore 'removed' and analogous to an immune class. However, Artzrouni and Gouteux also exclude these individuals as a source of blood so the removed class, R_h, does not contribute to infection and similarly, the total number of humans to feed from is decreased.

Consequently the force of infection onto the tsetse population is given by:

$$\frac{\alpha_1 p_{vh1} I_{h1}}{(S_{h1} + E_{h1} + I_{h1} + R_{h1})}$$

for Rogers and

$$\frac{\alpha_1 p_{vh1} I_{h1}}{(S_{h1} + E_{h1} + I_{h1})}$$

for Artzrouni and Gouteux. Similarly, the measured human prevalence is given by:

$$\frac{I_{h1}}{S_{h1} + E_{h1} + I_{h1} + R_{h1}}$$

for Rogers' model of progression and

$$\frac{I_{h1} + R_{h1}}{S_{h1} + E_{h1} + I_{h1} + R_{h1}}$$

for Artzrouni and Gouteux.

3.6 Modelling spatial heterogeneity

Tsetse and human populations are highly spatially structured. This spatial heterogeneity is not explicitly captured in any of the models developed using a differential equation approach; and these limitations were discussed in more detail by Peck and Bouyer [127]. The impact of spatial heterogeneity and tsetse/ human movement has long been recognised by the tsetse community (e.g. [185]) and by researchers investigating HAT (e.g. [35]). In many ways spatial structure makes disease more easy to control (if more difficult to model): 'hot spots' of locally-intense transmission may be identified and control efforts focussed on these populations and the riverine distribution of some tsetse species means that re-invasion after control efforts (the scourge of most control programmes) occur along predictable corridors.

One notable model that does attempt to incorporate this heterogeneity is the 'HAT-trick' model [150]. This is based on a 50×50 grid of 'habitat cells' each of which is characterised for its habitat and consequent effect on tsetse ecology, and the presence of animals and livestock. The user can overlay a habitat map on this grid, including riverine habitats, define tsetse ecology in each of the habitat types, allow migration between cells, and then impose control measures to gauge their impact on tsetse number, age-structure and HAT transmission. It is a highly sophisticated model, particularly on tsetse ecology, and its mapping functions make it appealing to policy makers who need to consider particular scenarios in detail. However, the main cost of this sophistication is that this model cannot generate the generic insights possible from a differential equation approach.

An analogous approach to incorporate spatial heterogeneity is to use agent-based modelling. This has become a fairly widespread technique in computer sciences with dedicated software suites for its implementation. In the current case, the 'agents' are humans and tsetse who move across a spatially structured environment while the simulation tracks their

individual properties such as age, infection status, and so on, as implemented by Muller *et al* [119]. As in HAT trick, the cost of this more realistic spatially-centred approach is the lack of insights that may be generated through a simpler tractable approach.

A final way of capturing spatial heterogeneity is through the use of meta-population models [65] where the populations of humans and vectors are split into semi-isolated sub-populations with movement between them; this can realistically reflect a fragmented habitat. The chief drawback of this approach is that tsetse populations may be structured but are rarely fragmented: the savannah form usually occur in large contiguous populations while the riverine tsetse species tend to be contiguous linear populations with extensive movement along rivers. Despite these restrictions, it remains a valuable attempt to understand spatial heterogeneity and may be useful in future situations as HAT nears extinction and the trypanosomes form semi-isolated populations.

3.7   Modelling tsetse fly population dynamics and seasonality

A useful measure of exposure for vector-born diseases is the entomological inoculation rate, or the number of infectious bites received per person per day. This is a compelling argument for linking disease transmission models to realistic vector population dynamics. To date, models focussing on HAT transmission have frequently ignored tsetse population dynamics completely (assuming fixed population sizes) [9, 56]), or have used simple models with some seasonal variation (e.g. [110, 141]); while more sophisticated models of tsetse fly population dynamics have been derived but have not been integrated with HAT models.

The components of a realistic population dynamics model and the dependency of the parameters to temperature and climate are fairly well defined [74]. One study linked the temperature-dependent life history traits of tsetse to an expression for R_0 in order to predict possible range expansions or contractions of Rhodesian HAT due to global climate change [116], although this was based on predicted mean annual temperatures rather than seasonal fluctuations.

It is not immediately obvious how important it is to include seasonal variation of tsetse abundance in HAT models, because although population sizes do vary considerably [143], this variation is relatively minor compared to that found in other vectors such as mosquitoes, where seasonality is often ignored despite its obvious importance. Additionally, the duration of infection in both humans and vectors is relatively long, which may temper the impact of seasonal variation.

It has been noted that there is significant variation in the seasonality of tsetse abundance between tsetse species, with certain species showing only moderate or barely any fluctuations and others, such as *G. morsitans submorsitans* vary considerably with resulting seasonal parasitaemia in mammalian hosts [110]. It is likely that seasonality influences HAT transmission in manners beyond fluctuations in tsetse abundance, for example through changes in agricultural activities that may affect human tsetse contact rates. Seasonality has subsequently been modelled through different means. For instance, Milligan and Baker incorporated seasonality by including a sinusoidal form for the emergence rate [110], while Rogers simulated the effects of seasonality by varying adult mortality and biting rates with temperature [144, 141] and Artzrouni and Gouteux used a linear relationship between temperature and emergence rate [14].

Mortality in juvenile stages also appears to have a seasonal component, but it may be that this represents a density-dependent effect instead [71, 128, 131]. Various other density-dependent effects have been included in tsetse models, for instance, Rogers [143] needed to include a form of density dependent mortality for both the adult and pupal stages in his population model to match field data. Density-dependent migration has also been included in models of tsetse dynamics [13]. A minimal population dynamics model including seasonality would therefore account for both temperature and density-dependent losses during the immature stages as well as the teneral phase.

Models that focused on the population dynamics of tsetse have been used to assess impact of natural factors (e.g. population density [143], environmental temperature [84]) and vector control [69] on the growth of tsetse populations (see review by Hargrove [74]). Other models have been developed to analyse the growth of open populations [185] by assuming logistic growth and diffusive movement of populations. This approach formed the basis of a series

of studies concerned with analysing the impact of various tsetse control operations [72, 81].

More recently, simulation models of tsetse populations have been developed to allow not only distribution, spread and abundance of tsetse to be modelled but also age-structure of the tsetse population [175]. These simulation models have been used to assess the likely impact and cost of insecticidal and sterile insect techniques (SIT) of vector control [175, 21, 82, 22, 23], impact of aerial spraying [98], insecticide-treated livestock [168] and the relative costs of tsetse control [151]. The 'Tsetse Muse' model's [175] outputs includes age structure and hence can be used to provide an indication of the density of tsetse that are old enough to be potential vectors. There is a need to combine these models with models of HAT transmission.

4 Model comparisons

We now explore an extended model formulation incorporating various elements of the models previously discussed (see Figure 13 for model outline and Figure 14 for simulation dynamics) to elucidate the effects of key parameters and model assumptions. In order to retain some sense of continuity, the model structure (with I_{hi} and R_{hi} corresponding in this case to first and second stage infection respectively) is used both here and in the previous Section 3.3 and the type of disease progression in the human population is that used by Artzrouni and Gouteux [10].

The total prevalence in the human population comprises individuals in both Stage I and II (even though only Stage I cases transmit infection to tsetse).

The model can be used to study the effect of certain parameters upon the endemic equilibrium. The two main variations in modelling have typically concerned:

- Host choice/preference and multi-host models including either secondary (reservoir) host populations, non-reservoir populations or a mixture of the two
- The teneral effect: models range from no teneral effect [56] through partial immunity [110] to full 'immunity' [141].

All other parameters are kept constant with values taken from Table 7.

4.1 Host preference

We assume that there are three species of mammalian hosts: humans, secondary reservoir hosts (which can transmit infection) and non-reservoir hosts. Additionally we assume that while the tsetses' host preference (s) is not explicitly known, it is possible to find the proportion of blood-meals taken from a certain host species (f_i) by analysis of blood meals. Here, f_1 corresponds to proportion of bloods meals on humans; f_2 to proportion of blood means on reservoir hosts; and f_3 to proportion of blood meals on all other hosts that are not part of the HAT transmission cycle; with $f_1 + f_2 + f_3 = 1$.

It is important to note that both the relative size of the secondary population and host preference will affect the prevalence of disease in the human population. Smaller reservoir host population sizes lead to more infection for the same proportion of blood feeding as there is more chance of the same reservoir host being bitten at least twice to complete its role in the transmission cycle. Conversely the size of the non-reservoir population is of no consequence if the proportion of blood meals taken is known. The relationship between secondary host population size, N_{h2}, the proportion of blood-meals taken from them f_2 and the prevalence in the human population at equilibrium is shown in Figure 15.

In these simulations we assume that a proportion, f_1, of blood-meals are from the human population and the remaining $f_2 + f_3 = 1 - f_1$ are from either the reservoir (f_2) or the non-reservoir (f_3) hosts. The results show that increasing f_2 increased the human prevalence. Funk *et al.* [56] and Rogers [141] found that without secondary reservoir hosts (equivalent to $f_2 = 0$), HAT infection cannot be sustained within the human population. The results here indicate that if the proportion of blood-feeding on humans is low (around 10% or less) then disease will become extinct in the absence of a reservoir animal population, however, if the proportion feeding on humans increases, a endemic state occurs even when $f_2 = 0$.

We note that a host prevalence of 20% or more is unnaturally high so it seems likely that $f_1 < 0.15$. Likewise many other parameter choices including large f_2 or low N_{h2} are unlikely due to the high levels of host infection they create.
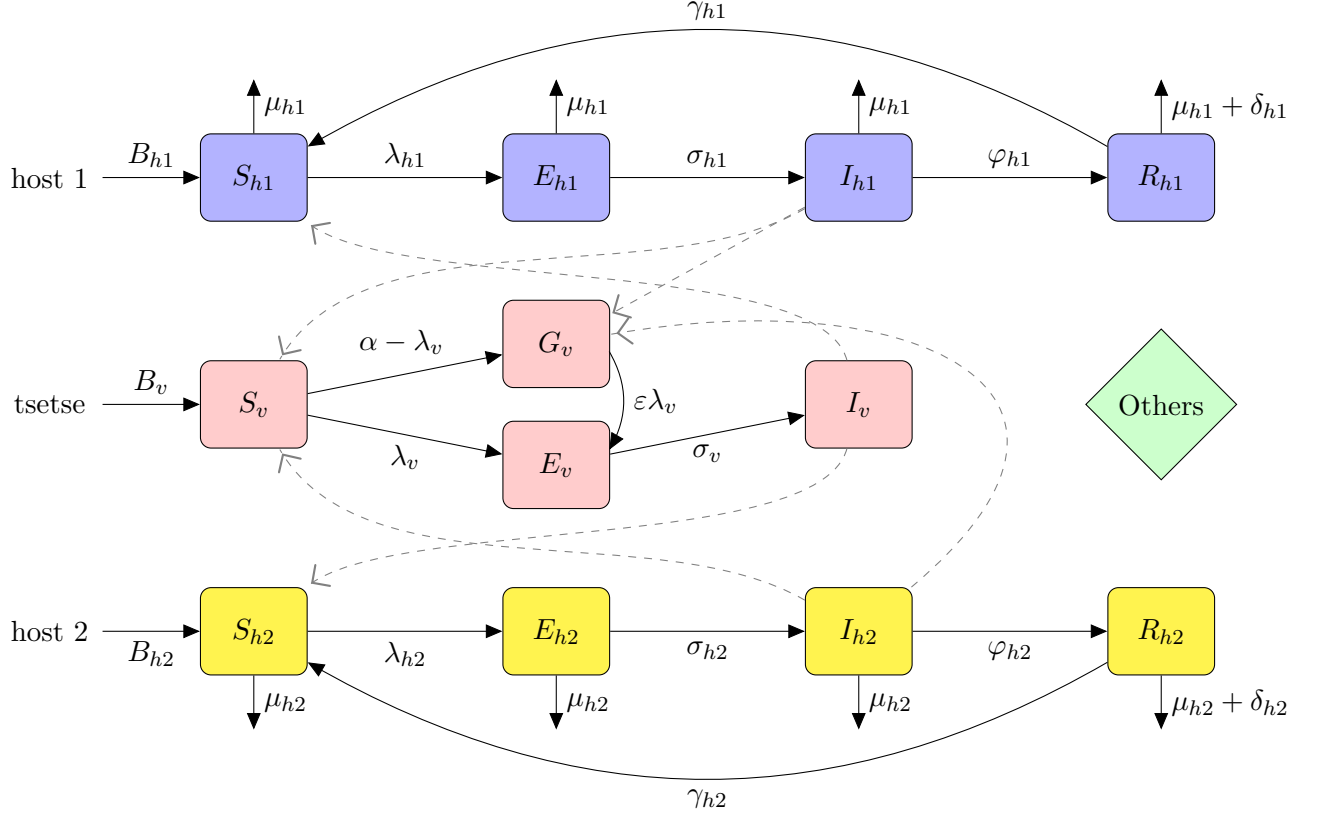
Figure 13: Interplay between the vectors and multiple host species. This model includes both reservoir (host 2) and non-reservoir (other) hosts in addition to humans (host 1) and tsetse. It is assumed that there are four possible infection status for hosts: susceptible, exposed, Stage I and Stage II. Upon entering Stage II, hosts are not infectious to tsetse through hospitalisation. Tsetse also have four stages corresponding to teneral flies, exposed flies, infectious flies and non-teneral non-infected flies. Non-teneral, non-infected tsetse have a reduced probability by a factor ε of becoming infected. Vector mortality which is at a constant per capita rate, μ_v out of all classes, regardless of infection or teneral status, is not shown. Dashed grey lines indicate transmission paths.

Endemic equilibria are highly sensitive to ratios of human to vectors and also humans to other hosts as well as the proportion of blood meals taken. As with all vector-borne disease models, the greater the ratio of vectors to hosts, the higher the disease prevalence/incidence. Likewise Figure 15 demonstrates how the endemic prevalence may be increased dramatically (from 0% to 40%) by just a small increase in secondary host feeding preference. This causes problems in reconciling model outputs with field observations that measured prevalence levels are extremely low (around 1% as compared to the values shown here).

4.2   Teneral effect

In order to study the effect of no, partial or full susceptibility of non-teneral tsetse, we vary the parameter ε. At $\varepsilon = 0$ full 'immunity' is acquired upon the first blood meal, whereas at $\varepsilon = 1$, all tsetse have the same susceptibility (similar to a standard Ross-Macdonald model.

Assuming that Gambian HAT is not zoonotic (no non-human bites lead to onward transmission) simulations (Figures 16a and 16b) show the relationship between ε and the equilibrium prevalence in humans. As intuition would dictate, prevalence in the human population increases as 'immunity' of non-teneral flies decreases. For a low proportion of bites upon humans, there are values of ε for which there is no positive endemic equilibrium, and values where one exists. As the feeding upon humans increases, even $\varepsilon = 0$ (no chance of infection after the first blood-meal) gives endemic prevalence.

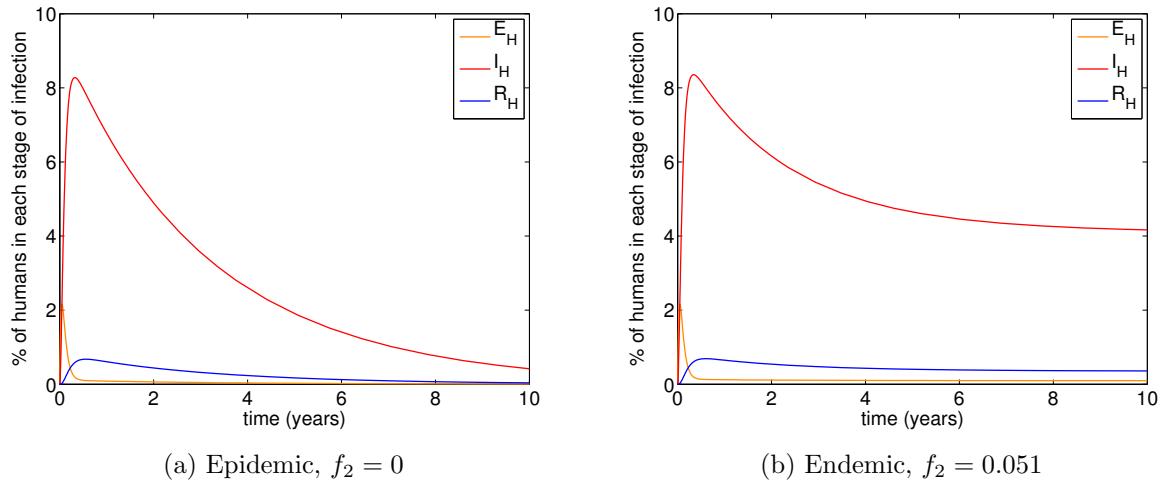(a) Epidemic, $f_2 = 0$ (b) Endemic, $f_2 = 0.051$

Figure 14: Examples of the possible dynamics generated by this model. Both simulations were run using $f_1 = 0.1$, $N_{h2} = 300$, and $\varepsilon = 0.05$. Initially all hosts were susceptible with 1% of tsetse infected. Figure (a), which shows an epidemic followed by eventual disease extinction (after around 50 years), was generated using $f_2 = 0$ as the secondary host feeding preference (i.e. all blood-meals not from humans were from non-reservoir species). Figure (b), which shows an initial peak in infection followed by an endemic level of infection, was generated using $f_2 = 0.051$. Throughout, the frequency of bites on the non-reservoir species is $f_3 = 1 - f_1 - f_2$.
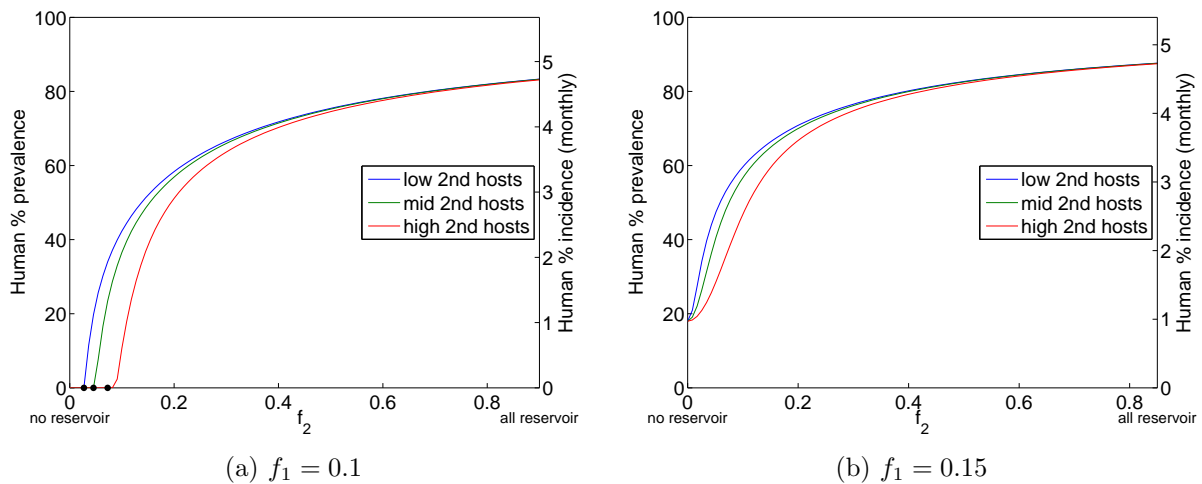

(a) $f_1 = 0.1$ (b) $f_1 = 0.15$

Figure 15: The relationship between host selection and human prevalence (or incidence) is shown for two choices of f_1. For each choice, the human population is fixed ($N_{h1} = 300$) and the secondary (reservoir) host population is varied in size, where 'low' represents $N_{h2} = 100$, 'mid' represents $N_{h2} = 300$ and 'high' represents $N_{h2} = 1000$. Bites not occurring on human or reservoir hosts arise from non-reservoir animals. In all cases shown, $\varepsilon = 0.05$ so non-teneral susceptibility is low and most new tsetse infections occur in teneral flies. The black dots show where the human prevalence/incidence drops to 0%.
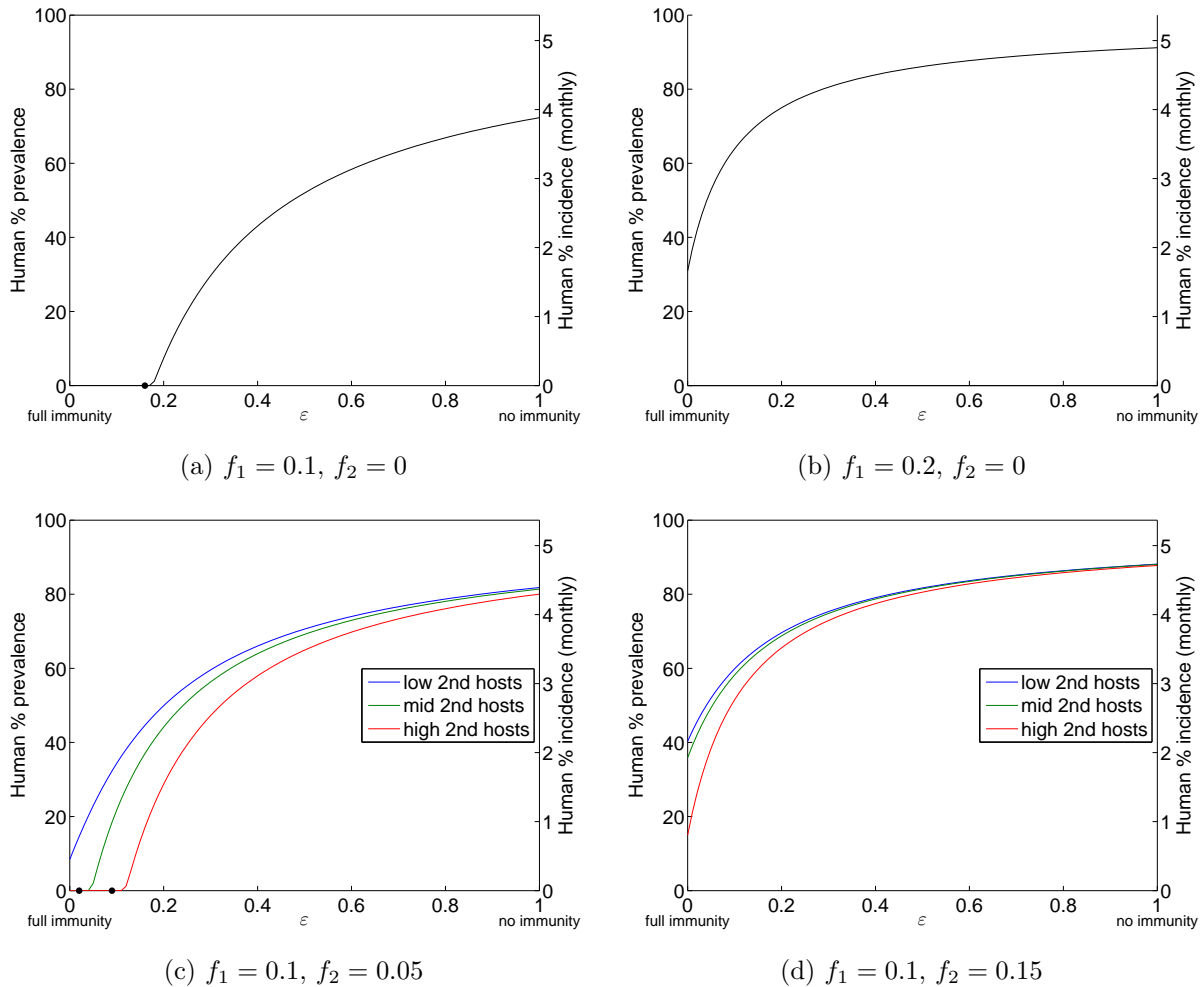
(a) $f_1 = 0.1$, $f_2 = 0$ (b) $f_1 = 0.2$, $f_2 = 0$

(c) $f_1 = 0.1$, $f_2 = 0.05$ (d) $f_1 = 0.1$, $f_2 = 0.15$

Figure 16: The relationship between the teneral effect parameter, ε, and human prevalence (or incidence) is shown for various choices of host preference. As in Figure 15, the remaining bites not taken on humans or secondary reservoir hosts occur on non-reservoir animals. In cases (a) and (b) there is no animal reservoir population.

If reservoir hosts are included (Figures 16c and 16d), the results are similar, but indicate how large an increase a secondary reservoir population could have on human prevalence.

Figure 16 shows that higher values of ε are unfeasible as host prevalence of 80% are never seen with any form of trypanosomiasis. From these results it would be expected that ε lies somewhere in the range 0–0.2. Likewise, since prevalence is usually very low, the results here indicate that $f_1 \geq 0.2$ is unrealistic, even if tsetse can only acquire infection upon their first blood-meal.

If $f_1 \leq 0.1$ and there are no reservoir hosts, then there must be some non-teneral flies which become infected since the disease cannot persist otherwise. The higher f_2 is, the lower ε needs to be to generate the same level of infection in the human population. In order to generate realistic low levels of prevalence in humans, it seems most likely that there is some low probability of non-teneral flies becoming infected and that at least a small proportion of bites occur upon a reservoir host population.

5 Models of control interventions and their cost-effectiveness

There are two main ways to control HAT: eliminate the infections in humans, or reduce tsetse fly densities and/or biting rates rates on humans. Tsetse densities and biting rates on humans can be reduced intentionally through vector control or a consequence of changes

in the densities and availability of non-human hosts. An important operational question is therefore to decide which is the more effective strategy and whether and how this choice depend on local HAT epidemiology.

Artzrouni and Gouteux [10] directly addressed this key operational issue of whether elimination can best be achieved by case detection in humans or by reducing tsetse numbers by control programmes. They developed a Ross-Macdonald type model (as described above), derived the basic reproductive number, R_0, for the model and examined which type of control, human or tsetse, would most easily push R_0 below 1. Their methodology is discussed in more detail in §5.1–5.2. They created an example showing that control measures depend on local epidemiology. In their model setting, Village A has high tsetse density but a small decrease in human duration of infectiousness would push HAT R_0 below 1. Conversely Village B has low tsetse numbers and a small decrease in their numbers would push HAT R_0 below 1. Their approach was to conclude that human screening and treatment would be favoured in Village A, while vector control would be more appropriate in Village B. There are likely to be other scenarios where both controls are necessary to control HAT and the optimal strategy is dependant upon parameterisation.

We consider this an important paper because it explicitly compares the different strategies and, importantly, relates them to local epidemiology. However, it is important to note that it has several important limitations in both its calibration and its model implementation. Its parameterisation took no account of how feasible it actually is to reduce the duration of human infectiousness compared to reducing tsetse density. Field data suggest tsetse number can be quickly reduced to very low levels so it is possible that this option is better even in villages where large reductions in tsetse numbers would be required to bring R_0 below 1. The problem inherent in its implementation is that it investigated equilibrium values with a simple target of $R_0 < 1$. In other words it had no time component and could not distinguish strategies that eliminate the epidemic in four weeks, from a policy that eliminates it in four years. Similarly it did not distinguish between a policy that reduces R_0 to 0.9 and one that reduces it to 0.1; if 100 people are currently infected, the first scenario would result in 90 new infections, while the second would lead to only 10 new cases.

The important message is that time is essential when controlling an epidemic and a rapid reduction in incidence (i.e. the number of new infection per unit time) is the main objective of an intervention rather that its long-term equilibrium conditions. We would argue that tsetse control and human screen and treat operate on very different time scales. Field data suggest tsetse numbers can be reduced to low levels over a very short period while humans screen and treat programs take significant periods of time to implement and that changes in the proportion of humans infectious takes a much longer period to decline. In many practical ways it is not an 'either/or' decision in an epidemic situation as it would be morally unacceptable to ignore humans infected in a HAT epidemic so human mass screen and treat will occur; we would argue that rapid deployment of focussed tsetse control be implemented as a priority because models suggest that changes in tsetse density and longevity of the magnitude achieved in previous interventions have the ability to rapidly reduce R_0 and hence incidence in the early stages on an epidemic. Vector control also has fewer logistical implications, fewer ethical implications (we cannot force people to be screened or to take the drugs), and appears to be much more cost effective. These considerations are invariably absent from simple models and we would argue that there is a clear research gap between the relatively large number of basic models already constructed based on equilibrium conditions and the operational research questions posed by the control community which have a clear temporal element.

5.1 Detection and treatment of humans

The detection and treatment of cases in humans has been a primary control strategy for HAT. Cases can be detected through either large-scale screening programmes which occur periodically or via continuous (but smaller-scale) screening at health care centres.

The simplest way to model continuous detection and treatment is to assume that this increases the exit rate, φ_{h1} from the infectious stage (I_{h1}), although the manner in which the intervention will affect this parameter must be considered. Artzrouni and Gouteux [10] formulate a model with a new parameter, C_h that is the monthly percent detection of stage

I cases. If the parameter φ_{h1}, the rate of movement of infectious individuals (Stage I) to recovered individuals (Stage II), is considered to be a composite of the intrinsic underlying disease progression and the removal rate by treatment (extrinsic) such that:

$$\varphi_{h1} = \varphi_{\text{int}} + \varphi_{\text{ext}} \tag{5.1}$$

then the monthly percent detection is given by:

$$C_h = 100\left[1 - \exp\left(-30\varphi_{\text{ext}}\right)\right] \tag{5.2}$$

(Note that in this paper under their parameterisation, rates are given with the unit of time taken as 3 days rather than 1). Consequentially, the exit rate from the class I_{h1} is given by:

$$\varphi_{h1} = \varphi_{\text{int}} - \frac{1}{30}\ln\left(1 - \frac{C_h}{100}\right) \tag{5.3}$$

Now that φ_{h1} is written as a function of the monthly percent detection, it can easily be seen that linear changes in detection do not produce linear changes in φ_{h1}.

This type of approach yields a meaningful way in which the parameter φ_{h1} may be controlled and the impact of such a control method upon both the disease dynamics or upon the basic reproductive ratio (R_0) can now be explored. Artzrouni and Gouteux [10] examine the effect of altering the monthly percent detection (in addition to another control) upon R_0 to find the threshold at which disease no longer occurs ($R_0 = 1$) in terms of this controllable parameter C_h.

We note however, that this assumption of incorporating the treatment rate into φ_{hi} is only valid for analysis of R_0 and not for model simulations or equilibrium values because in Artzrouni and Gouteux's formulation, all humans in R_h, including the newly detected ones, experience an additional disease mortality rate (corresponding to Stage II disease). A more consistent formulation would be include an additional class of detected and treated humans.

5.2 Control of tsetse

Whilst there are several methods to control tsetse, such as aerial spraying and the deployment of natural or artificial baits, there are essentially three governing parameters for tsetse populations: the number of tsetse N_v, the birth rate B_v and the death rate μ_v. It is not hard to see that these are interlinked – if the birth rate were reduced, it would be expected that the population size would also fall. Likewise controls which reduce the population size (such as trapping) essentially increase a tsetse's daily mortality.

Modelling work, in some tsetse control scenarios, has made the assumption that altering tsetse mortality only changes the flux through the system rather than the population size, in this case the birth rate would have to increase in order for the system to equilibrate at the same level as before or, more likely, there is some natural relocation of tsetse from other areas to retain the original population size.

Artzrouni and Gouteux [10] model tsetse control in this way; hypothesising that tsetse controls will affect mortality but not population size. In a similar fashion to modelling treatment of humans (described in Section 5.1) the vector death rate μ_v is considered to comprise of two parts: the underlying 'natural' mortality experienced by tsetse in their environment $\mu_{v,int}$ and an additional death rate, $\mu_{v,ext}$, imposed by some control strategy such that:

$$\mu_v = \mu_{v,int} + \mu_{v,ext} \tag{5.4}$$

This death rate is related to the daily percentage of flies killed, denoted here by C_v, by:

$$C_v = 100\left[1 - \exp(-\mu_{v,ext})\right] \tag{5.5}$$

(in the paper, Artzrouni and Gouteux use rates with 3 days as the unit of time, so their equations account for this) and so:

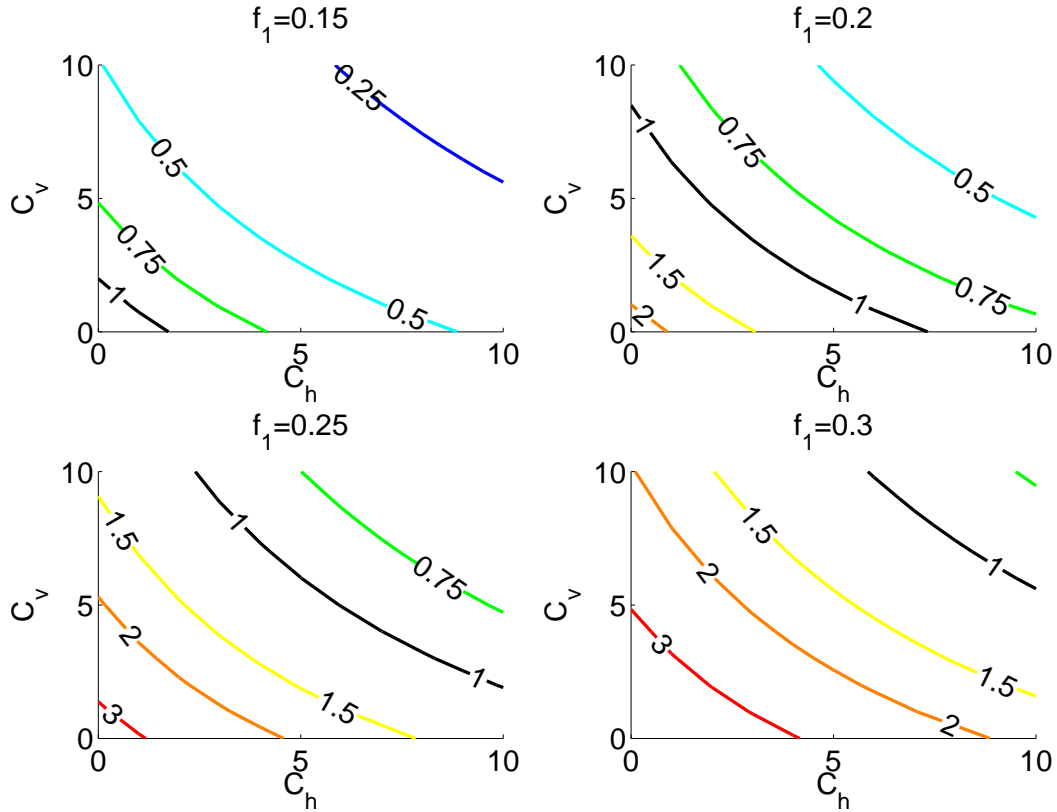$$\mu_v = \mu_{v,int} - \ln\left(1 - \frac{C_v}{100}\right) \tag{5.6}$$

Figure 17: The plots show level sets of R_0 for various values above and below the $R_0 = 1$ threshold (shown in black). To the right of and above the $R_0 = 1$ contour, disease will die out, to the left of and below, there will be either an epidemic or endemic scenario. C_h is the monthly percentage of detection and treatment of humans. C_v is the daily percentage of tsetse killed.

This, along with the corresponding formulation for φ_{h1}, were used by Artzrouni and Gouteux [10] to examine the expected change in R_0 as the two controllable parameters C_h (treatment of asymptomatic humans) and C_v (killing of tsetse) are varied.

Here similar results are reproduced with the same methodology, but with parameter values as defined in Table 3.2. Simulation results show that with this parameterisation, when the proportion of bites on humans is low, $f_1 \leq 0.1$, R_0 is always less than one. Figure 17 demonstrates how, as the percentage of bites taken upon huamns is increased, increased control efforts are needed to eliminate HAT transmission. As f_1 becomes larger, the more unlikely it is that a single strategy alone will not be sufficient to control and eliminate HAT.

Other modelling work on control of tsetse flies has focused on the tsetse population alone. Hargrove [75] used stochastic branching process theory to predict the impact of control measures on tsetse populations. As tsetse population numbers become low, stochastic effects will dominate both population extinction and the timescale over which this may occur. Hargrove uses two key controllable parameters: adult (female) tsetse daily mortality (referred to as Δ but is similar to C_v) and the probability of a successfully mating with a fertile male, η. The latter may be controlled through the introduction of sterile males into the population, known as the Sterile Insect Technique (SIT).

Results produced by Hargrove have indicated that if the probability of insemination is less than 10%, the population will become extinct. However SIT is more costly than other methods such as trapping, so it likely to be more cost-effective to use trapping alone or in combination with SIT. Additionally, the increase in adult tsetse mortality due to trapping would reduces the time to extinction, even if it would eventually occurs with SIT alone.

5.3   Paratransgenesis

Theoretical work has been done to investigate the potential use of tsetse symbionts for trypanosomiasis control based on paratransgenesis [3, 108]. Paratransgenesis relies on the ability to genetically modify one of the tsetse symbionts to release an effector molecule that would inhibit trypanosomes within the vector. Genetic modification of *Sodalis* has been accomplished, and its distribution within the tsetse midgut would allow for the effector to be expressed in a relevant location where it can interact with the pathogen. One suggestion has been to use *W. pipientis* as a drive mechanism to allow for a population replacement strategy, which would hinge on the effector and drive mechanism not becoming disassociated over time. The potential for using *W. pipientis* as a drive mechanism was brought into focus when Alam *et al* [3] revealed that *Wolbachia*, as in mosquitoes, induces cytoplasmic incompatibility in tsetse: eggs fertilized by a male harbouring a different strain of *Wolbachia* result in greatly reduced larval deposition. Further, *Wolbachia* was thought to result in a fitness benefit to tsetse, in addition to the benefits associated with *Wigglesworthia*.

The authors constructed a continuous time model of the proportion of *Wolbachia*-infected tsetse which led to the two major conclusions that *Wolbachia* is likely to reach fixation from any initial release ratio, due to the fitness benefits associated with the bacteria, and that the time to fixation is relatively short, a median of 529 days in their simulations. The latter result may depend on the assumption that females remain receptive to mates throughout life. Although remating is thought to be common in tsetse, mating with more than 2-3 males is unlikely, and remating may be most common in the first few days of life [76].

These issues were addressed in a follow-up study [108], where age-structure was incorporated into the model in 10 day increments and mating assumed to occur within the first, with a proportion of females mating a second time. The spread of *Wolbachia* was hampered only if the females that had mated with an incompatible male, remated. This population dynamics model was linked to a HAT transmission model, corresponding to that of Rogers [141]. The teneral period during which tsetse are susceptible was taken as 24 hours. The results indicated that HAT prevalence would decrease at a rate comparable to the spread of the transgene, and depended on the initial release ratio. Multiple tsetse species being present, while only one is targeted by the transgenic release was not found to be a major impediment to the interruption of transmission, unless the secondary species was present at a proportion greater than circa 15%.

Although enticing as an additional tool in the arsenal against African trypanosomiasis, a key consideration will have to be whether such population replacement strategies can be more cost-effective than other control methods. Although our understanding of the microsymbionts of tsetse, their occurrence in field populations, impacts on tsetse susceptibility to trypanosomes and associated fitness costs or benefits, has developed greatly (though many questions remain) since the modelling study by Baker *et al* [19], our understanding of the role of these symbionts on HAT epidemiology remains limited.

6   Outlook

The many models summarised here have demonstrated the variety of ways that modelling HAT can be approached. For *T. b. gambiense* some of the key modelling themes have been the potential existence and effect of animal reservoir populations upon human disease prevalence and the impact of teneral susceptibility upon disease transmission. However there are distinct gaps as would be expected for any neglected tropical disease. Some of the issues that need addressing in future work are highlighted here.

6.1   Transient disease dynamics

Most models of HAT published in the literature are derived and given as systems of ODEs (and sometimes DDEs) which may be solved to yield temporal disease dynamics, but temporal behaviour is rarely discussed. Instead, the primary focus of the literature has been the final endemic equilibrium state rather than changes in transmission over time or capturing epidemic dynamics.

Over 95% of human cases of HAT occur for Gambian HAT in foci where there are often small epidemics rather than a stable endemic situation, so it is important that models are able to encapsulate both sets of behaviour. A clear gap in the understanding of Gambian HAT is the generation of these foci and so studying the temporal dynamics rather than solely equilibria is crucial.

Even in endemic situations, if control strategies are executed, it is crucial to understand the time-scale over which measures will take effect and for how long such controls will need to be implemented. Until this is known, it is impossible to determine the potential cost of an intervention. Fortunately, the type of models already developed provide a suitable starting point from which to hypothesise the impact and time-scale of control upon disease dynamics. These temporal, rather than equilibrium, considerations are vital in choosing optimal control strategies as discussed above in §5.

6.2 Tsetse fly biting

At present, the impact of the frequency and timing of vector-bites upon disease prevalence is not well understood. Most HAT models rely on the Ross-Macdonald-type force of infection generated by using a mean time between bites and assuming these times are exponentially distributed.

Some work by Hargrove and Williams, however, addressed this problem by creating suitable models for patterns of tsetse feeding [83]. Hargrove and Williams performed cost-benefit analysis by assuming only that tsetse must replicate themselves in order for the population to survive using the knowledge that around three blood-meals are needed during pregnancy to produce a viable larva. Other work, based upon field data of tsetse caught in odour-baited traps, used the amount of blood in the tsetse's gut as a proxy for the time since last blood-meal, by fitting to an ODE metabolism model [80].

These type of feeding models must now be integrated into disease models in order to discern the interaction of bite distribution and human disease prevalence and control.

6.3 Age structure in tsetse flies

It has long been known that, like other vectors such as the mosquito, tsetse do not have constant mortality. Hargrove [78] proposed that tsetse exhibit a 'U-shaped' mortality function of the form:

$$\mu_v(a) = k_1 \left[k_2 \exp(-k_2 a) + k_3 \exp(k_3 a) \right] \tag{6.1}$$

where k_1, k_2, k_3 are constants and a is age. This function was formulated using mark-recapture data and was shown to be a good fit to wild flies [78].

The impact of vector senescence upon disease transmission has been explored for the mosquito [30], however there are currently no such studies for the tsetse. Mortality patterns in mosquitoes have been found to increase with age and be described well by Gompertz functions [39], or logistic functions [159]. It is possible that under certain field situations, a higher mortality for newly emerged mosquitoes also occurs as it does for tsetse: for instance, Lyimo and Takken [102] found that the average size of newly emerged female *Anopheles gambiae* s.l. was significantly smaller than that of indoor-resting females, suggesting a higher mortality for smaller females in the days following emergence, while in nectar-deprived situations, early life mortality is increased [158], in which case Weibull functions described mortality patterns best. Bellan [30] found that the basic 'constant mortality' assumption overestimated the impact of control strategies which reduce mosquito survival since constant mortality consistently overestimates vectorial capacity [48, 159]. It is difficult to say if the same qualitative effects would be true for the tsetse as it has a different age-dependent mortality and, additionally for HAT, the teneral phenomenon needs to be incorporated. This highlights a need for more work in this area.

It is important to note the interchangeable use of the terms 'teneral', 'unfed' and 'susceptible' throughout the literature. These are not necessarily synonymous; it has been shown that tsetse susceptibility to trypanosome infection or the 'teneral effect' is correlated with age [177]. Susceptibility to trypanosomes has been shown to decrease with age upon emergence, however if pushed to starvation, older tsetse can experience an increase in susceptibility. In order for models to truly capture the 'teneral phenomenon', the effects of age, feeding status

and starvation upon susceptibility must first be disentangled. Future modelling work with age-structured tsetse populations would be capable of exploring waning susceptibility as a function of age rather than (or in addition to) whether they have fed or not.

Ultimately the way in which teneral susceptibility is modelled must be biologically motivated to generate a true picture of its effects upon disease transmission and prevalence, and here agent-based models which track the state of individual tsetse may be more appropriate.

6.4   Existence of foci and heterogeneity

Models are only as good as the assumption upon which they are based, which in turn reflect our knowledge of the underlying biology and epidemiology of the disease. There are two features of HAT epidemiology which are not fully explained, and remain an area for future research: (i) low prevalence rates in hosts and tsetse flies, and (ii) spatially stable disease foci of the gambiense form.

Gambiense HAT infection is overwhelmingly restricted to about 300 disease foci that have been historically stable over the last 150 years. The underlying reasons for their existence and stability remains a matter of speculation. One putative explanation is the presence of an animal reservoir in these foci that sustain the disease in humans as supported by Funk *et al.* [56]. Alternatively a more effective, cryptic vector species or sub-species may be present in these foci. The problem with both these suggestions is that the foci have remained stable despite the huge environmental changes that have occurred over the last 150 years and it seems a reasonable assumption that such widespread changes would have led to the elimination of some foci and the creation of some new ones. In general foci are spatially stable with the notable exception of SE Uganda where movement of livestock has led to movement of foci [54]. Additionally, many experienced field biologists have studied HAT in these foci and have not noted any environmental similarities between the foci that would support the contention of a local animal reservoir or tsetse sub-species.

The second epidemiological factor is the low prevalence of HAT in both the human and tsetse. It is generally necessary to dissect around 4 000 tsetse before finding an infection. Molecular detection techniques are more sensitive, but even under these conditions, the prevalence of gambiense remains remarkably low. Infection rates in humans may occasionally go as high as 10% as noted in a very large epidemic in Uganda but generally the prevalence rates peak at around 1 or 2% in a human epidemic. There are several ways of reconciling the observations. There may be a large amount of heterogeneity in transmission such that most people are extremely unlikely to become infected while the highly exposed (and susceptible) sub-population are all infected. Most infectious diseases are heterogeneous but the scale of the heterogeneity required to explain a prevalence of 1–2%, suggests that other factors may also be responsible. However, although most trypanosomiases models have included multiple host species, with a few exceptions (such as Muller *et al.* [119]), they have assumed homogeneous host populations within each species. This implies that each human is equally likely to get bitten and subsequently get infected and contract the disease and ignores the substantial heterogeneity in HAT transmission between villages and within villages. Also, no mathematical models have accounted for trypanotolerance, which was recently shown in humans [91] where some proportion of the population can be infectious for multiple years before self-curing and returning to a susceptible stage.

Further model development, either through individual based models, spatially explicit models, or metapopulation models are needed to understand the role of population heterogeneity and spatial structure in HAT transmission dynamics. This should lead to an improved understanding of the reasons for the existence and persistence of HAT transmission foci, may explain why mathematical models frequently overestimate prevalence of infection in humans and tsetse flies, and could point to more efficient strategies for HAT control and elimination.

6.5   Stochastic models

The majority of HAT models have been deterministic in nature. Exceptions are Muller *et al.* [119] who showed that prevalence in humans is sensitive to human densities and the initial number of infected flies, implying sensitivity to initial conditions; and Hargrove [75] who examined tsetse population extinctions using a stochastic framework but did not explicitly include disease.

As control programmes further reduce prevalence and elimination becomes the goal, the effects of individual level and low probability events will become even more important. Stochastic models will become even more necessary to help map out a path towards elimination, and additionally to find explanations for localised disease take-offs and extinctions in individual foci, which are characteristic of the Gambian form of HAT.

6.6 Toward predictive models of HAT

Mathematical models of infectious diseases come in a wide variety ranging from more general, tractable models that by necessity make vast simplifying assumptions, to more complex simulation-based models that are more closely tied to the biology of the system and possess greater predictive power, at the cost of analytical tractability. Most HAT models to date lean toward the more general models, often including simplifications such as assuming perfect mixing of vectors and hosts; using a prevalence-based rather than an infection burden-based approach to modelling infection; ignoring density-dependence in parasite establishment or uptake; and assuming exponential exit rates for most, if not all, compartments. One area where these models have struggled is in capturing the incredibly low prevalence rates in humans that are typically recorded in the field, where 1% prevalence is considered as very high. For *T. b. gambiense*, Rogers predicted an equilibrium prevalence of 7% in humans, 28.7% in non-human animals, and 0.61% in tsetse (Rogers 1988 [141]). Fitting this model to age-prevalence curves resulted in seemingly unrealistic estimates, for instance the duration of infection was estimated as high as 58 years, and each human expected to receive a bite only once every four years (Rogers 1989 [142]). Artzrouni & Gouteux (1996) [9] mention this as a justification for the development of their compartmental model. Although they, unlike Rogers, find that R_0 can be greater than 1 in the absence of animal reservoirs, the equilibrium prevalence predicted by their model is far higher than that of Rogers. The nullclines of their collapsed model when assuming there are 3 000 tsetse biting 300 humans in a village are depicted in Figure 18 (redrawn from their paper), show equilibrium values at 0% for humans and tsetse, and 67% infection in humans and 1% in tsetse. Like Rogers, their estimate for the duration of infection was short at 4 months, which they based on the average duration during an epidemic in Niari, Congo. Adjusting this to the current (longer) estimates for the duration of gambiense HAT would shift the non-trivial equilibrium to even higher prevalence levels.

A later paper used a similar model but with different fly death rates, human population sizes, and allowed immigration of tsetse to predict ranges of prevalence of infection in humans between 13–48% (Artzrouni & Gouteux (2001) [11]). An agent-based model that incorporated a greater amount of biological detail nevertheless predicted prevalence ranging from 10–16% in simulations modelled after the Bipindi focus (Muller, Grebaut & Gouteux [119]), only dropping to 4–5% prevalence when assuming a short Stage I duration of 4–12 months. Funk *et al.* (2013) [56], based on a susceptible-infected-susceptible model, found that under an assumption of random mixing they could only recreate realistic prevalence patterns (1.2% prevalence in humans) when allowing for animal reservoirs, in line with Rogers (1988) [141]. However, they also showed that a human-vector only cycle without reservoir hosts was possible in their model under fairly strong heterogeneous exposure to bites.

Further investigations on the impact of the simplifying assumptions present in HAT models and model fitting and validation exercises appear the way forward, though a bottleneck may be the availability of high quality field data on infection rates in humans, animals and vectors.
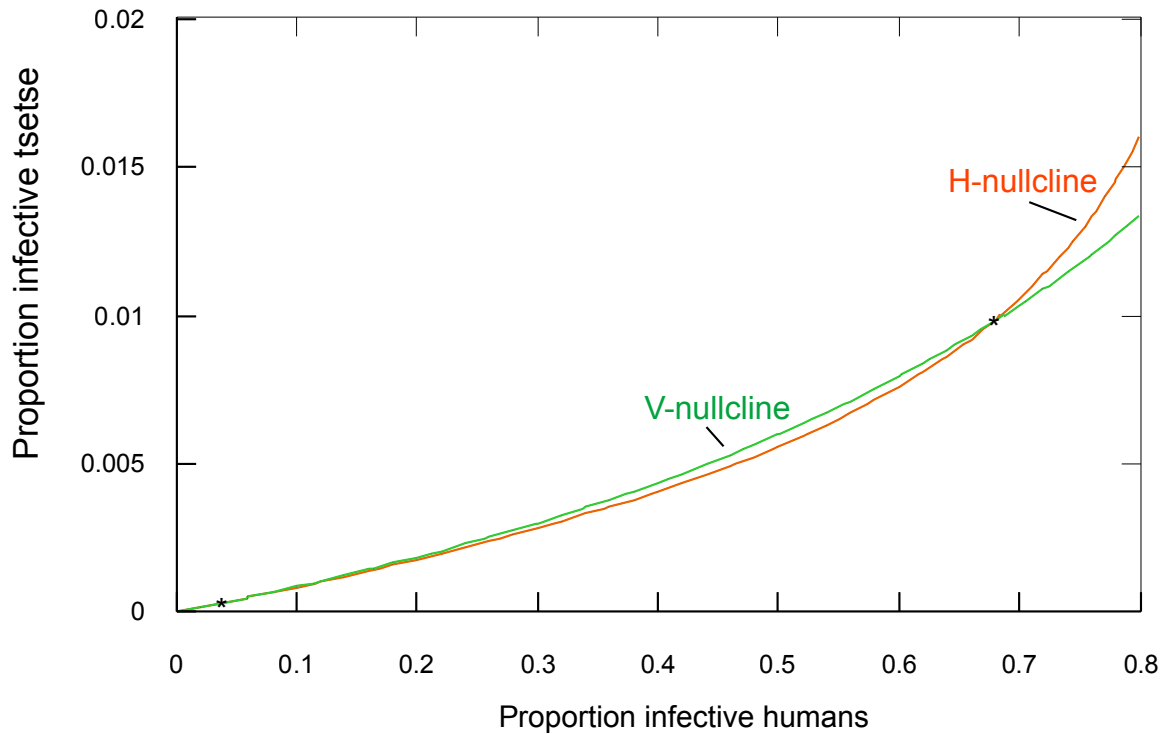
Figure 18: Nullclines for the simplified two-variable (infective humans and tsetse) model of Artzrouni & Gouteux (1996) [9], at a vector:human ratio of 10:1 and their specified parameter values. Redrawn from Artzrouni & Gouteux (1996). The red line indicates values where $\mathrm{d}i_h/\mathrm{d}t = 0$, and the green line where $\mathrm{d}i_v/\mathrm{d}t = 0$. There are three equilibrium points: trivial (0,0), unstable (0.039, 0.00032), and stable (0.67, 0.0097). This accentuates an issue with the predictive ability of HAT models lacking an animal reservoir, heterogeneity, or other modifications, as the unstable equilibrium point at 3.9% prevalence in humans would be considered a epidemic situation with extremely high prevalence in reality.

Acknowledgements

References

[1] K Akoda, P V D Bossche, E A Lyaruu, and R D Deken. Maturation of a *Trypanosoma brucei* infection to the infectious metacyclic stage is enhanced in nutritionally stressed tsetse flies. *Journal of Medical Entomology*, 6(46):1446–1449, 2009.

[2] S Aksoy. Sleeping sickness elimination in sight: time to celebrate and reflect, but not relax. *PLoS Neglected Tropical Diseases*, 2011.

[3] U Alam, J Medlock, C Brelsfoard, R Pais, C Lohs, S Balmand, J Carnogursky, A Heddi, P Takac, A P Galvani, and S Aksoy. Wolbachia symbiont infections induce strong cytoplasmic incompatibility in the tsetse fly *Glossina morsitans*. *PLoS Pathogens*, 7(12):e1002415, December 2011.

[4] R Allsopp and B H Hursey. Insecticidal control of tsetse. In I Maudlin, P H Holmes, and M A Miles, editors, *The Trypanosomiases*. CABI, Wallingford, 2004.

[5] C Amongi, K Picozzi, R Selby, N A Wardrop, L Hamill, A Kakembo, C Waiswa, J D Kabasa, and S C Welburn. Stamping out sleeping sickness in Uganda: evaluation of 31 months' interventions targeted at the cattle reservoir of disease. *Tropical Medicine and International Health*, 16, 2011.

[6] R. M. Anderson and R. M. May. *Infectious diseases of humans: dynamics and control.* Oxford Unversity Press, Oxford, 1991.

[7] F I C Apted. Clinical manifestations and diagnosis of sleeping sickness. *The African Trypanosomiases*, 1970.

[8] J. L. Aron and R. M. May. The population dynamics of malaria. In R. M. Anderson, editor, *The population dynamics of infectious disease: theory and applications*, pages 139–179. Chapman and Hall, London, 1982.

[9] M. Artzrouni and J.-P. Gouteux. A compartmental model of sleeping sickness in central africa. *Journal of Biological Systems*, 4(4):459–477, 1996.

[10] M. Artzrouni and J.-P. Gouteux. Control strategies for sleeping sickness in Central Africa: a model-based approach. *Tropical Medicine and International Health*, 1(6):753–764, December 1996.

[11] M. Artzrouni and J.-P. Gouteux. A model of Gambian sleeping sickness with open vector populations. *Mathematical Medicine and Biology*, 18(2):99–117, 2001.

[12] M. Artzrouni and J.-P. Gouteux. Population dynamics of sleeping sickness: A microsimulation. *Simulation and Gaming*, 32(2):215–227, 2001.

[13] M. Artzrouni and J.-P. Gouteux. Estimating tsetse population parameters: application of a mathematical model with density-dependence. *Medical and Veterinary Entomology*, 17(3):272–279, 2003.

[14] M. Artzrouni and J.-P. Gouteux. A parity-structured matrix model for tsetse populations. *Mathematical Biosciences*, 204(2):215–231, 2006.

[15] M T Ashcroft, E Burtt, and H Fairbairn. The experimental infection of some African wild animals with *Trypanosoma rhodesiense*, *T. brucei* and *T. congolense*. *Annals of Tropical Medicine and Parasitology*, 53:147–161, May 1959.

[16] R W Ashford. What it takes to be a reservoir host. *Belgian Journal of Zoology (Belgium)*, October 1997.

[17] H K Auty, I Malele, S Cleaveland, P Raj, and T Lembo. Host feeding preferences of tsetse (Glossina swynnertoni and Glossina pallidipes) in Serengeti National Park, Tanzania. *PLoS Neglected Tropical Diseases*.

[18] H K Auty, K Picozzi, I Malele, S J Torr, S Cleaveland, and S C Welburn. Using molecular data for epidemiological inference: Assessing the prevalence of *Trypanosoma brucei rhodesiense* in tsetse in Serengeti, Tanzania. *PLoS Neglected Tropical Diseases*, 6(1):e1501, January 2012.

[19] R D Baker, I Maudlin, P J M Milligan, D H Molyneux, and S C Welburn. The possible role of Rickettsia-like organisms in trypanosomiasis epidemiology. *Parasitology*, 100(02):209, 1990.

[20] H J Barclay and J W Hargrove. Probability models to facilitate a declaration of pest-free status, with special reference to tsetse (Diptera: Glossinidae). *Bulletin of Entomological Research*, 95(1):1–11, February 2005.

[21] H J Barclay and M J B Vreysen. A dynamic population model for tsetse (Diptera: Glossinidae) area-wide integrated pest management. *Population ecology*, 2011.

[22] H J Barclay and M J B Vreysen. Conclusions from a dynamic population model for tsetse: response to comments. *Population ecology*, 2011.

[23] H J Barclay and M J B Vreysen. The interaction of dispersal and control methods for the riverine tsetse fly Glossina palpalis gambiensis (Diptera: Glossinidae): a modelling study. *Population ecology*, 2013.

[24] M P Barrett, I M Vincent, R J S Burchmore, A J N Kazibwe, and E Matovu. Drug resistance in human African trypanosomiasis. *Future Microbiology*, 6(9):1037–1047, September 2011.

[25] J D Barry and R McCulloch. Antigenic variation in trypanosomes: enhanced phenotypic variation in a eukaryotic parasite. *Advances in Parasitology*, 49:1–70, January 2001.

[26] M Baylis and A L Mbwabi. The feeding success of tsetse flies, *Glossina pallidipes* (Diptera: Glossinidae), on oxen treated with pyrethroid pour-ons at Galana Ranch, Kenya. *Bulletin of Entomological Research*, 1994.

[27] M Baylis and A L Mbwabi. Feeding behaviour of tsetse flies (*Glossina pallidipes austen*) on Trypanosoma-infected oxen in Kenya. *Parasitology*, 110 (Pt 3):297–305, March 1995.

[28] M Baylis and C O Nambiro. The effect of cattle infection by *Trypanosoma congolense* on the attraction, and feeding success, of the tsetse fly *Glossina pallidipes*. *Parasitology*, 1993.

[29] M M Baylis. The daily feeding rate of tsetse (Diptera: Glossinidae) on cattle at Galana Ranch, Kenya and comparison with trypanosomiasis incidence. *Acta Tropica*, 65(2):81–96, May 1997.

[30] S E Bellan. The importance of age dependent mortality and the extrinsic incubation period in models of mosquito-borne disease transmission and control. *PLoS One*, 5(4):e10165, 2010.

[31] J Bouyer, M Pruvot, Z Bengaly, P M Guerin, and R Lancelot. Learning influences host choice in tsetse. *Biology Letters*, 3(2):113–117, April 2007.

[32] R. Brun, J. Blum, R. Chappuis, and C. Burri. Human African trypanosomiasis. *The Lancet*, 375(9709):148–159, January 2010.

[33] R Brun, R Don, R T Jacobs, M Z Wang, and M P Barrett. Development of novel drugs for human African trypanosomiasis. *Future Microbiology*, 6(6):677–691, June 2011.

[34] C Burri, A Stich, and R Brun. Current Chemotherapy of Human African Trypanosomiasis. In I Maudlin, P H Holmes, and M A Miles, editors, *The Trypanosomiases*. CABI, Wallingford, 2004.

[35] K. Chalvet-Monfray, M. Artzrouni, J.-P. Gouteux, P. Auger, and P. Sabatier. A two-patch model of Gambian sleeping sickness: application to vector control strategies in a village and plantations. *Acta Biotheoretica*, 46(3):207–222, 1998.

[36] F Checchi, J A N Filipe, M P Barrett, and D Chandramohan. The natural progression of Gambiense sleeping sickness: What is the evidence? *PLoS Neglected Tropical Diseases*, 2(12):e303, December 2008.

[37] F Checchi, J A N Filipe, D T Haydon, D Chandramohan, and F Chappuis. Estimates of the duration of the early and late stage of gambiense sleeping sickness. *BMC Infectious Diseases*, 8(1):16–16, January 2008.

[38] P-H Clausen, I Adeyemi, B Bauer, M Breloeer, F Salchow, and C Staak. Host preferences of tsetse (Diptera: Glossinidae) based on bloodmeal identifications. *Medical and Veterinary Entomology*, 12(2):169–180, March 1998.

[39] A N Clements and G D Paterson. The analysis of mortality and survival rates in wild populations of mosquitoes. *Journal of Applied Ecology*, 18:373–399, 1981.

[40] J F Corson. The infections produced in sheep and antelopes by a strain of Trypanosoma rhodesiense. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 33(1):37–46, June 1939.

[41] CF Curtis and AM Jordan. Calculations of the productivity of *Glossina austeni* newst. maintained on goats and on lop-eared rabbits. *Bulletin of entomological research*, 59(04):651–658, 1970.

[42] C Dale, S C Welburn, I Maudlin, and P J M Milligan. The kinetics of maturation of trypanosome infections in tsetse. *Parasitology*, 111:187–191, January 1995.

[43] H Davies. Further eradication of tsetse in the Chad and Gongola river systems in north-eastern Nigeria. *Journal of Applied Ecology*, 8:563–578, 1971.

[44] S. Davis, S. Aksoy, and A. Galvani. A global sensitivity analysis for African sleeping sickness. *Parasitology*, 138(4):516–526, April 2011.

[45] S Deborggraeve and P Büscher. Recent progress in molecular diagnosis of sleeping sickness. *Expert Review of Molecular Diagnostics*, 12(7):719–730, September 2012.

[46] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28:365–382, 1990.

[47] O Diekmann, J A P Heesterbeek, and M G Roberts. The construction of next-generation matrices for compartmental epidemic models. *Journal of The Royal Society Interface*, 7(47):873–885, April 2010.

[48] K Dietz. Mathematical models for transmission and control of malaria. pages 1091–1133. Malaria: principles and practice of malariology, 1988.

[49] R D Dransfield, R Brightwell, C Kyorku, and B Williams. Control of tsetse fly (Diptera: Glossinidae) populations using traps at Nguruman, south-west Kenya. *Bulletin of Entomological Research*, 80(03):265, July 2009.

[50] R Du Toit. Trypanosomiasis in Zululand and the control of tsetse flies by chemical means. *Onderstepoort Journal of Veterinary Research*, 26:317–387, 1954.

[51] R H Dwinger, J G Grootenhuis, M Murray, S K Moloo, and G Gettinby. Susceptibility of buffaloes, cattle and goats to infection with different stocks of *Trypanosoma vivax* transmitted by *Glossina morsitans centralis*. *Research in Veterinary Science*, 41(3):307–315, November 1986.

[52] N A Dyer, C Rose, N O Ejeh, and A Acosta-Serrano. Flying tryps: survival and maturation of trypanosomes in tsetse flies. *TRENDS in Parasitology*, 29(4):188–196, April 2013.

[53] M C Eisler, S J Torr, P G Coleman, N Machila, and J F Morton. Integrated control of vector-borne diseases of livestock–pyrethroids: panacea or poison? *TRENDS in Parasitology*, 19(8):341–345, July 2003.

[54] E M Fèvre, P G Coleman, M Odiit, J W Magona, S C Welburn, and M E Woolhouse. The origins of a new *Trypanosoma brucei rhodesiense* sleeping sickness outbreak in eastern Uganda. *Lancet*, 358(9282):625–628, August 2001.

[55] E M Fèvre, K Picozzi, J G Jannin, S C Welburn, and I Maudlin. Human African trypanosomiasis: Epidemiology and control. *Advances in Parasitology*, 61:167–221, January 2006.

[56] S. Funk, H. Nishiura, H. Heesterbeek, W. J. Edmunds, and F. Checchi. Identifying transmission cycles at the human-animal interface: The role of animal reservoirs in maintaining Gambiense human African trypanosomiasis. *PLoS Computational Biology*, 9(1):e1002855, 2013.

[57] C. Garrett-Jones. Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature*, 204(4964):1173–1175, December 1964.

[58] G Gibson and S J Torr. Visual and olfactory responses of haematophagous Diptera to host stimuli. *Medical and Veterinary Entomology*, 13(1):2–23, February 1999.

[59] J P Glasgow. The feeding habits of *Glossina swynnertoni Austen*. *The Journal of Animal Ecology*, 1961.

[60] J P Glasgow. The distribution and abundance of tsetse. *The Distribution and Abundance of Tsetse*, 1963.

[61] J G Grootenhuis, R H Dwinger, R B Dolan, S K Moloo, and M Murray. Susceptibility of African buffalo and Boran cattle to *Trypanosoma congolense* transmitted by *Glossina morsitans centralis*. *Veterinary Parasitology*, 35(3):219–231, March 1990.

[62] J. D. F. Habbema, G. J. van Oortmarssen, and A. P. Plaisier. The ONCHOSIM model and its use in decision support for river blindness control. In V. Isham and G. Medley, editors, *Models for infectious human diseases: Their structure and relation to data*, pages 360–380. Cambridge University Press, 1996.

[63] F Hackett, L Berrang Ford, E Fèvre, and P Simarro. Incorporating scale dependence in disease burden estimates: The case of human African trypanosomiasis in Uganda. *PLoS Neglected Tropical Diseases*, 8(2):e2704, February 2014.

[64] L R Haines. Examining the tsetse teneral phenomenon and permissiveness to trypanosome infection. *Frontiers in Cellular and Infection Microbiology*, 3:84–84, January 2013.

[65] I. A. Hanski and O. E. Gaggiotti, editors. *Ecology, Genetics and Evolution of Metapopulations: Standard Methods for Inventory and Monitoring*. Elsevier Academic Press, 2004.

[66] J W Hargrove. Some changes in the flight apparatus of tsetse flies, *Glossina morsitans* and *G. pallidipes*, during maturation. *Journal of Insect Physiology*, 21(8):1485–1489, July 1975.

[67] J W Hargrove. The effect of human presence on the behaviour of tsetse (*Glossina* spp.) (Diptera, Glossinidae) near a stationary ox. *Bulletin of Entomological Research*, 1976.

[68] J W Hargrove. Tsetse dispersal reconsidered. *Journal of Animal Ecology*, 50:351–373, 1981.

[69] J W Hargrove. Tsetse: the limits to population growth. *Medical and Veterinary Entomology*, 2(3):203–217, June 1988.

[70] J W Hargrove. Towards a general rule for estimating the stage of pregnancy in field-caught tsetse flies. *Physiological Entomology*, 1995.

[71] J. W. Hargrove. Reproductive abnormalities in tsetse flies in zimbabwe. *Entomologia Experimentalis et Applicata*, 92(1):89–99, 1999.

[72] J. W. Hargrove. A theoretical study of the invasion of cleared areas by tsetse flies (Diptera: Glossinidae). *Bulletin of Entomological Research*, 90:201–209, 2000.

[73] J W Hargrove. *Tsetse eradication: sufficiency, necessity and desirability.* DFID Animal Health Programme, Centre for Tropical Veterinary Medicine, 2003.

[74] J. W. Hargrove. Tsetse population dynamics. In I. Maudlin, P. H. Holmes, and M. A. Miles, editors, *The Trypanosomiases*, pages 113–138. CABI Publishing, Oxfordshire, UK, 2004.

[75] J W Hargrove. Extinction probabilities and times to extinction for populations of tsetse flies Glossina spp. (Diptera: Glossinidae) subjected to various control measures. *Bulletin of Entomological Research*, 95(1):13–21, February 2005.

[76] J W Hargrove. Age-specific changes in sperm levels among female tsetse (*Glossina* spp.) with a model for the time course of insemination. *Physiological Entomology*, 37(3):278–290, July 2012.

[77] J W Hargrove, M T P Holloway, and G A Vale. Catches of tsetse (*Glossina* spp.) (Diptera: Glossinidae) from traps and targets baited with large doses of natural and synthetic host odour. *Bulletin of Entomological Research*, 1995.

[78] J W Hargrove, R Ouifki, and J E Ameh. A general model for mortality in adult tsetse (*Glossina* spp.). *Medical and Veterinary Entomology*, 25(4):385–394, March 2011.

[79] J. W. Hargrove, R. Ouifki, D. Kajunguri, G. A. Vale, and S. J. Torr. Modeling the control of trypanosomiasis using trypanocides or insecticide-treated livestock. *PLoS Neglected Tropical Diseases*, 6(5):e1615, May 2012.

[80] J W Hargrove and M J Packer. Nutritional states of male tsetse flies (*Glossina* spp.) (Diptera: Glossinidae) caught in odour-baited traps and artificial refuges: models for feeding and digestion. *Bulletin of Entomological Research*, 83:29–46, 1993.

[81] J W Hargrove, S J Torr, and H M Kindness. Insecticide-treated cattle against tsetse (Diptera: Glossinidae): what governs success? *Bulletin of Entomological Research*, 93(3):203–217, May 2003.

[82] J W Hargrove, S J Torr, and G A Vale. Comment on Barclay and Vreysen: published dynamic population model for tsetse cannot fit field data. *Population ecology*, 2011.

[83] J W Hargrove and B G Williams. A cost-benefit analysis of feeding in female tsetse. *Medical and Veterinary Entomology*, 9:109–119, 1995.

[84] J. W. Hargrove and B. G. Williams. Optimized simulation as an aid to modelling, with an application to the study of a population of tsetse flies, *Glossina morsitans morsitans* (Diptera: Glossinidae). *Bulletin of entomological research*, 88(04):425–435, 1998.

[85] D T Haydon, S Cleaveland, and L H Taylor. Identifying reservoirs of infection: a conceptual and practical challenge. *Emerging Infectious Diseases*, 2002.

[86] R. C. Heaversedge. Levels of insect parasitism in puparia of glossina morsitans orientalis vanderplank (diptera) in rhodesia. *Entomol Soc Southern Afr J*, 32:231–235, 1969.

[87] C A Hoare. *The trypanosomes of mammals. A zoological monograph.* Blackwell Scientific Publications, 1972.

[88] A Hoppenheit, B Bauer, S Steuber, W Terhalle, O Diall, K-H Zessin, and P-H Clausen. Multiple host feeding in *Glossina palpalis gambiensis* and *Glossina tachinoides* in southeast Mali. *Medical and Veterinary Entomology*, 27(2):222–225, May 2013.

[89] C H N Jackson. The causes and implications of hunger in tsetse-flies. *Bulletin of Entomological Research*, 1933.

[90] C H N Jackson. The hunger-cycles of *Glossina morsitans Westwood* and *G. swynnertoni Austen*. *The Journal of Animal Ecology*, 1954.

[91] V. Jamonneau, H. Ilboudo, J. Kaboré, D. Kaba, M. Koffi, P. Solano, A. Garcia, D. Courtin, C. Laveissière, K. Lingue, P. Büscher, and B. Bucheton. Untreated human infections by *Trypanosoma brucei gambiense* are not 100% fatal. *PLoS neglected tropical diseases*, 6(6):e1691, 2012.

[92] V Jamonneau, S Ravel, M Koffi, and D Kaba. Mixed infections of trypanosomes in tsetse and pigs and their epidemiological significance in a sleeping sickness focus of Cote d'Ivoire. *Parasitology*, 129(06):693–702, December 2004.

[93] A M Jordan. Tsetse eradication plans for southern Africa. *Parasitology Today*, 1(5):121–123, January 1985.

[94] A M Jordan. *Trypanosomiasis control and African rural development.* Longman Group Ltd., 1986.

[95] AM Jordan and CF Curtis. Productivity of *Glossina austeni* newst. maintained on lop-eared rabbits. *Bulletin of Entomological Research*, 58(02):399–410, 1968.

[96] AM Jordan and CF Curtis. Productivity of *Glossina morsitans morsitans* westwood maintained in the laboratory, with particular reference to the sterile-insect release method. *Bulletin of the World Health Organization*, 46(1):33, 1972.

[97] K Kappmeier, E M Nevill, and R J Bagnall. Review of tsetse flies and trypanosomosis in South African. *Onderstepoort Journal of Veterinary Research*, (65):195–203, 1998.

[98] P M Kgori, S Modo, and S J Torr. The use of aerial spraying to eliminate tsetse from the Okavango Delta of Botswana. *Acta Tropica*, 2006.

[99] C Kubi, J van den Abbeele, R de Deken, T Marcotty, P Dorny, and P van den Bossche. The effect of starvation on the susceptibility of teneral and non-teneral tsetse flies to trypanosome infection. *Medical and Veterinary Entomology*, 20(4):388–392, December 2006.

[100] P A Langley and R Wall. The implications of hunger in the tsetse fly, *Glossina pallidipes*, in relation to its availability to trapping techniques. *Journal of Insect Physiology*, 1990.

[101] S G A Leak. *Tsetse biology and ecology: their role in the epidemiology and control of trypanosomosis.* CABI, 1999.

[102] E O Lyimo and W Takken. Effects of adult body size on fecundity and the pre-gravid rate of *Anopheles gambiae* females in Tanzania. *Medical and Veterinary Entomology*, 7(4):328–332, 1993.

[103] G. Macdonald. The analysis of infection rates in diseases in which superinfection occurs. *Tropical Diseases Bulletin*, 47:907–915, 1950.

[104] G. Macdonald. The analysis of the sporozoite rate. *Tropical Diseases Bulletin*, 49:569–585, 1952.

[105] I Maudlin. African trypanosomiasis. *Annals of Tropical Medicine and Parasitology*, 100(8):679–701, December 2006.

[106] I Maudlin and C H Green. The potential for insecticide resistance in *Glossina* (Diptera: Glossinidae) – an investigation by computer simulation and chemical analysis. *Bulletin of Entomological Research*, 71:691–702, 1981.

[107] I Maudlin, P H Holmes, and M A Miles, editors. *The Trypanosomiases*. CABI, Wallingford, 2004.

[108] J. Medlock, K. E. Atkins, D. N. Thomas, S. Aksoy, and A. P. Galvani. Evaluating paratransgenesis as a potential control strategy for African trypanosomiasis. *PLoS Neglected Tropical Diseases*, 7(8):e2374, 2013.

[109] D Mehlitz, U Zillmann, and C M Scott. Epidemiological studies on the animal reservoir of Gambiense sleeping sickness. Part III. Characterization of trypanozoon stocks by isoenzymes and sensitivity to human serum. *Tropenmedizin und Parasitologie*, 33(2):113–118, 1982.

[110] P. J. M. Milligan and R. D. Baker. A model of tsetse-transmitted animal trypanosomiasis. *Parasitology*, 96(1):211–239, 1988.

[111] P Mitashi, E Hasker, V Lejon, V Kande, J-J Muyembe, P Lutumba, and M Boelaert. Human African trypanosomiasis diagnosis in first-line health services of endemic countries, a systematic review. *PLoS Neglected Tropical Diseases*, 6(11):e1919, November 2012.

[112] S K Moloo, R O Olubayo, J M Kabata, and I O Okumu. A comparison of African buffalo, N'Dama and Boran cattle as reservoirs of Trypanosoma congolense for different Glossina species. *Medical and Veterinary Entomology*, 6(3):225–230, June 1992.

[113] S K Moloo, G O Orinda, C L Sabwa, S H Minja, and R A Masake. Study on the sequential tsetse-transmitted *Trypanosoma congolense*, *T. brucei brucei* and *T. vivax* infections to African buffalo, eland, waterbuck, N'Dama and Boran cattle. *Veterinary Parasitology*, 80(3):197–213, January 1999.

[114] S K Moloo, C L Sabwa, and M Baylis. Feeding behaviour of *Glossina pallidipes* and *G. morsitans centralis* on Boran cattle infected with *Trypanosoma congolense* or *T. vivax* under laboratory conditions. *Medical and Veterinary Entomology*, 14(3):290–299, August 2000.

[115] S K Moloo, C L Sabwa, and J M Kabata. Vector competence of *Glossina pallidipes* and *G. morsitans centralis* for *Trypanosoma vivax*, *T. congolense* and *T. b. brucei*. *Acta Tropica*, 51(3-4):271–280, July 1992.

[116] S. Moore, S. Shrestha, K. W. Tomlinson, and H. Vuong. Predicting the effect of climate change on African trypanosomiasis: integrating epidemiology with parasite and vector biology. *Journal of the Royal Society Interface*, 9(70):817–830, 2012.

[117] L J Morrison, P Majiwa, A F Read, and J D Barry. Probabilistic order in antigenic variation of *Trypanosoma brucei*. *International Journal for Parasitology*, 35(9):961–972, August 2005.

[118] A F Mulla and L R Rickman. How do African game animals control trypanosome infections? *Parasitology Today*, 4(12):352–354, December 1988.

[119] G. Muller, P. Grébaut, and J.-P. Gouteux. An agent-based model of sleeping sickness: simulation trials of a forest focus in southern Cameroon. *Comptes Rendus Biologies*, 327(1):1–11, 2004.

[120] M Murray. Factors affecting duration and intensity of trypanosome infection of domestic animals. *Annales de la Societe belge de medecine tropicale*, 69:189–184, January 1989.

[121] H Nishiura, B Hoye, M Klaassen, and S Bauer. How to find natural reservoir hosts from endemic prevalence in a multi-host population: A case study of influenza in waterfowl. *Epidemics*, 1(2):118–128, 2009.

[122] Z Njagu, S Mihok, E Kokwaro, and D Verloo. Isolation of it Trypanosoma brucei from the monitor lizard (*Varanus niloticus*) in an endemic focus of Rhodesian sleeping sickness in Kenya. *Acta Tropica*, 72(2):137–148, March 1999.

[123] F Njiokou, C Laveissière, G Simo, and S W Nkinin. Wild fauna as a probable animal reservoir for *Trypanosoma brucei gambiense* in Cameroon. *Infection*, 6(2):147–153, 2006.

[124] Elaine O Nsoesie, John S Brownstein, Naren Ramakrishnan, and Madhav V Marathe. A systematic review of studies on forecasting the dynamics of influenza outbreaks. *Influenza and other respiratory viruses*, 8(3):309–316, 2014.

[125] M O Omolo, A Hassanali, S Mpiana, J Esterhuizen, J Lindh, M J Lehane, P Solano, J B Rayaisse, G A Vale, S J Torr, and I Tirados. Prospects for developing odour baits to control *Glossina fuscipes* spp., the major vector of human African trypanosomiasis. *PLoS Neglected Tropical Diseases*, 3(5):e435–e435, January 2009.

[126] L Peacock, S Cook, V Ferris, M Bailey, and W Gibson. The life cycle of *Trypanosoma (Nannomonas) congolense* in the tsetse fly. *Parasites & Vectors*, 5(1):109–109, January 2012.

[127] S. L. Peck and J. Bouyer. Mathematical modeling, spatial complexity, and critical decisions in tsetse control. *Journal of Economic Entomology*, 105(5):1477–1486, 2012.

[128] R. J. Phelps and P. M. Burrows. Lethal temperatures for puparia of *glossina morsitans orientalis*. *Entomologia experimentalis et applicata*, 12(1):23–32, 1969.

[129] R J Phelps and P M Burrows. Prediction of the pupal duration of *Glossina morsitans orientalis Vanderplank* under field conditions. *Journal of Applied Ecology*, 1969.

[130] R J Phelps and P M Burrows. Puparial duration in *Glossina morsitans orientalis* under conditions of constant temperature. *Entomologia Experimentalis et Applicata*, 12(1):33–43, April 1969.

[131] R. J. Phelps and G. P. Y. Clarke. Seasonal elimination of some size classes in males of *Glossina morsitans morsitans* Westw.(Diptera, Glossinidae). *Bulletin of Entomological Research*, 64(02):313–324, 1974.

[132] R J Phelps and G A Vale. Studies on populations of *Glossina morsitans morsitans* and *G. pallidipes* (Diptera: Glossinidae) in Rhodesia. *Journal of Applied Ecology*, 1978.

[133] S E Randolph and D J Rogers. Feeding cycles and flight activity in field populations of tsetse (Diptera:Glossinidae). *Bulletin of Entomological Research*, 68(04):655, 1978.

[134] S E Randolph and D J Rogers. Trap-catches, nutritional condition and the timing of activity of the tsetse fly *Glossina longipennis* (Diptera: Glossinidae). *Bulletin of Entomological Research*, 1991.

[135] S E Randolph, B G Williams, D J Rogers, and H Connor. Modelling the effect of feeding-related mortality on the feeding strategy of tsetse (Diptera: Glossinidae). *Medical and Veterinary Entomology*, 6(3):231–240, June 1992.

[136] S Ravel, D Patrel, M Koffi, V Jamonneau, and G Cuny. Cyclical transmission of *Trypanosoma brucei gambiense* in *Glossina palpalis gambiensis* displays great differences among field isolates. *Acta Tropica*, 2006.

[137] J B Rayaisse, I Tirados, D Kaba, S Y Dewhirst, J G Logan, A Diarrassouba, E Salou, M O Omolo, P Solano, M J Lehane, J A Pickett, G A Vale, S J Torr, and J Esterhuizen. Prospects for the development of odour baits to control the tsetse flies *Glossina tachinoides* and it G. palpalis s.l. *PLoS Neglected Tropical Diseases*, 4(3):e632, March 2010.

[138] R. C. Reiner, , T. A. Perkins, C. M. Barker, T. Niu, L. F. Chaves, A. M. Ellis, D. B. George, A. Le Menach, J. R. C. Pulliam, D. Bisanzio, C. Buckee, C. Chiyaka, D. A. T. Cummings, A. J. Garcia, M. L. Gatton, P. W. Gething, D. M. Hartley, G. Johnston, E. Y. Klein, E. Michael, S. W. Lindsay, A. L. Lloyd, D. M. Pigott, W. K. Reisen, N. Ruktanonchai, B. K. Singh, A. J. Tatem, U. Kitron, S. I. Hay, T. W. Scott, and D. L. Smith. A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010. *Journal of the Royal Society Interface*, 10(81):20120921, 2013.

[139] M G Roberts and J A P Heesterbeek. A new method for estimating the effort required to control an infectious disease. *Proceedings of the Royal Society B: Biological Sciences*, 270(1522):1359–1364, July 2003.

[140] D Rogers. Study of a natural population of *Glossina fuscipes fuscipes* Newstead and a model of fly movement. *The Journal of Animal Ecology*, 1977.

[141] D. J. Rogers. A general model for the African trypanosomiases. *Parasitology*, 97(1):193–212, August 1988.

[142] D. J. Rogers. The development of analytical models for human trypanosomiasis. *Annales de la Société Belge de Médecine Tropicale*, 69(Suppl. 1):73–88, 1989.

[143] D. J. Rogers. A general model for tsetse populations. *Insect Science and Its Application*, 11(3):331–346, 1990.

[144] D J Rogers and S E Randolph. Local variation in the population dynamics of *Glossina palpalis palpalis* (Robineau-Desvoidy) (Diptera: Glossinidae). I. Natural population regulation. *Bulletin of Entomological Research*, 1984.

[145] D J Rogers and S E Randolph. Detection of activity cycles of tsetse from capture–recapture data. *Ecological Entomology*, 1986.

[146] D J Rogers and S E Randolph. Estimation of rates of predation on tsetse. *Medical and Veterinary Entomology*, 4(2):195–204, April 1990.

[147] R. Ross. *The prevention of malaria*. John Murray, London, 2 edition, 1911.

[148] R Ross. An application of the theory of probabilities to the study of a priori pathometry. Part I. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 92(638):204–230, February 1916.

[149] F R Rurangirwa, A J Musoke, V M Nantulya, C C Nkonge, L L Njuguna, E Z Mushi, L L Karstad, and J J Grootenhuis. Immune effector mechanisms involved in the control of parasitaemia in *Trypanosoma brucei*-infected wildebeest (*Connochaetes taurinus*). *Immunology*, 58(2):231–237, May 1986.

[150] S Torr and G Vale and C Mangwiro and C Laveissiere and D Hall and J Morton and B van Munster and J Hargrove. HAT Trick. websitehttp://www.tsetse.org/trick/. Accessed: 15/05/14.

[151] A P M Shaw, S J Torr, C Waiswa, G Cecchi, G R W Wint, R C Mattioli, and T P Robinson. Estimating the costs of tsetse control options: An example for Uganda. *Preventive Veterinary Medicine*, 110(3-4):290–303, June 2013.

[152] P P Simarro, G Cecchi, J R Franco, M Paone, A Diarra, J A Ruiz-Postigo, E M Fèvre, R C Mattioli, and J G Jannin. Estimating and mapping the population at risk of sleeping sickness. *PLoS Neglected Tropical Diseases*, 6(10):e1859–e1859, January 2012.

[153] P P Simarro, J G Jannin, and P Cattand. Eliminating human African trypanosomiasis: where do we stand and what comes next? *PLoS Medicine*, 5(2):e55–e55, February 2008.

[154] G Simo, T Asonganyi, S W Nkinin, F Njiokou, and S Herder. High prevalence of *Trypanosoma brucei gambiense* group 1 in pigs from the Fontem sleeping sickness focus in Cameroon. *Veterinary Parasitology*, 139(1-3):57–66, June 2006.

[155] D. L. Smith, K. E. Battle, S. I. Hay, C. M. Barker, T. W. Scott, and F. E. McKenzie. Ross, Macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. *PLoS Pathogens*, 8(4):e1002588, 2012.

[156] P Solano, S J Torr, and M J Lehane. Is vector control needed to eliminate gambiense human African trypanosomiasis? *Frontiers in Cellular and Infection Microbiology*, 3, 2013.

[157] D Steverding. The history of African trypanosomiasis. *Parasites & Vectors*, 1(1), February 2008.

[158] C M Stone, B T Jackson, and W A Foster. Effects of plant-community composition on the vectorial capacity and fitness of the malaria mosquito *Anopheles gambiae*. *The American journal of tropical medicine and hygiene*, 87(4):727–736, October 2012.

[159] L M Styer, J R Carey, and J L Wang. Mosquitoes do senesce: departure from the paradigm of constant mortality. *The American Society of Tropical Medicine and Hygiene*, 76(1):111–117, 2007.

[160] The malERA Consultative Group on Modeling. A research agenda for malaria eradication: Modeling. *PLoS Medicine*, 8:e1000403, 1 2011.

[161] S J Torr. Responses of tsetse flies (Diptera: Glossinidae) to warthog (*Phacochoerus aethiopicus* Pallas). *Bulletin of Entomological Research*, 84(03):411–419, July 2009.

[162] S J Torr, A Chamisa, T N Clemen Mangwiro, and G A Vale. Where, when and why do tsetse contact humans? Answers from studies in a national park of Zimbabwe. *PLoS Neglected Tropical Diseases*, 6(8):e1791–e1791, January 2012.

[163] S J Torr and J W Hargrove. Factors affecting the landing and feeding responses of the tsetse fly *Glossina pallidipes* to a stationary ox. *Medical and Veterinary Entomology*, 12(2):196–207, March 1998.

[164] S J Torr, J W Hargrove, and G A Vale. Towards a rational policy for dealing with tsetse. *TRENDS in Parasitology*, 21(11):537–541, November 2005.

[165] S J Torr, I Maudlin, and G A Vale. Less is more: restricted application of insecticide to cattle to improve the cost and efficacy of tsetse control. *Medical and Veterinary Entomology*, 21(1):53–64, March 2007.

[166] S J Torr, A Prior, P J Wilson, and S Schofield. Is there safety in numbers? The effect of cattle herding on biting risk from tsetse flies. *Medical and Veterinary Entomology*, 21(4):301–311, December 2007.

[167] S J Torr and P Solano. Olfaction in Glossina–host interactions: a tale of two tsetse. Olfaction in Vector-host Interactions, 2010.

[168] S. J. Torr and G. A. Vale. Is the even distribution of insecticide-treated cattle essential for tsetse control? Modelling the impact of baits in heterogeneous environments. *PLoS Neglected Tropical Diseases*, 5(10):e1360, October 2011.

[169] D A Turner and T K Golder. Susceptibility to topical applications of endosulfan and dieldin in sprayed and unsprayed populations of *Glossina pallidipes* Austen (Diptera: Glossinidae) in Kenya. *Bulletin of Entomological Research*, 76:519–527, 1986.

[170] G A Vale. The responses of tsetse flies (Diptera: Glossinidae) to mobile and stationary baits. *Bulletin of Entomological Research*, 1974.

[171] G A Vale. Feeding responses of tsetse flies (Diptera: Glossinidae) to stationary hosts. *Bulletin of Entomological Research*, 1977.

[172] G A Vale, J W Hargrove, P Solano, F Courtin, and J B Rayaisse. Explaining the host-finding behavior of blood-sucking insects: computerized simulation of the effects of habitat geometry on tsetse fly movement. *PLoS Neglected Tropical Diseases*.

[173] G A Vale, D F Lovemore, S Flint, and G F Cockbill. Odour-baited targets to control tsetse flies, *Glossina* spp. (Diptera: Glossinidae), in Zimbabwe. *Bulletin of Entomological Research*, 78(01):31–49, March 1988.

[174] G A Vale and S J Torr. Development of bait technology to control tsetse. In *The Trypanosomiases*, pages 509–523. CABI, Wallingford, 2004.

[175] G A Vale and S J Torr. User-friendly models of the costs and efficacy of tsetse control: application to sterilizing and insecticidal techniques. *Medical and Veterinary Entomology*, 19(3):293–305, August 2005.

[176] M J Vreysen, K M Saleh, M Y Ali, A M Abdulla, Z R Zhu, K G Juma, V A Dyck, A R Msangi, P A Mkonyi, and H U Feldmann. Glossina austeni (Diptera: Glossinidae) eradicated on the island of Unguja, Zanzibar, using the sterile insect technique. *Journal of Economic Entomology*, 93(1):123–135, February 2000.

[177] D P Walshe, M J Lehane, and L R Haines. Post eclosion age predicts the prevalence of midgut trypanosome infections in *Glossina*. *PLoS One*, 6(11):e26984, November 2011.

[178] D P Walshe, C P Ooi, M J Lehane, and L R Haines. The Enemy Within: Interactions Between Tsetse, Trypanosomes and Symbionts. In *Advances in Insect Physiology*, pages 119–175. Academic Press, 2009.

[179] S C Welburn and I Maudlin. Tsetse–trypanosome interactions: Rites of passage. *Parasitology Today*, 15(10):399–403, October 1999.

[180] S C Welburn and I Maudlin. Priorities for the elimination of sleeping sickness. *Advances in Parasitology*, 79:299–337, January 2012.

[181] S C Welburn, I Maudlin, and P J M Milligan. Trypanozoon: infectivity to humans is linked to reduced transmissibility in tsetse I. Comparison of human serum-resistant and human serum-sensitive field isolates. *Experimental parasitology*, 1995.

[182] S C Welburn, K Picozzi, P G Coleman, and C Packer. Patterns in age-seroprevalence consistent with acquired immunity against *Trypanosoma brucei* in Serengeti lions. *PLoS Neglected Tropical Diseases*, 2(12):e347–e347, January 2008.

[183] WHO. Control and surveillance of human African trypanosomiasis. Technical Report 984, November 2013.

[184] L P M Willemse. A trial of odour baited targets to control the tsetse fly, Glossina morsitans centralis (Diptera: Glossinidae) in west Zambia. *Bulletin of Entomological Research*, 81(3):351–357, September 1991.

[185] B. Williams, R. Dransfield, and R. Brightwell. The control of tsetse flies in relation to fly movement and trapping efficiency. *Journal of Applied Ecology*, 29:163–179, 1992.

[186] C M Wombou Toukam, P Solano, Z Bengaly, V Jamonneau, and B Bucheton. Experimental evaluation of xenodiagnosis to detect trypanosomes at low parasitaemia levels in infected hosts. *Parasite*, 18(4):295–302, November 2011.

[187] World Health Organization. Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation. 2012. WHO/HTM/NTD/2012.2.

[188] World Health Organization. Control and surveillance of human African trypanosomiasis. *World Health Organization Technical Report Series*, 2013.

[189] World Health Organization 2012. Accelerating work to overcome the global impact of neglected tropical diseases – A roadmap for implementation. `http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf`. Accessed: 31/04/14.