SENIOR HONORS THESIS: SEASONAL FLUCTUATION IN TSETSE FLY POPULATIONS AND CONTROL STRATEGIES FOR HUMAN AFRICAN TRYPANOSOMIASIS: A MATHEMATICAL MODEL

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Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, is an endemic public health threat to Sub-Saharan Africa with an estimated 55 million people at risk. Classified by the World Health Organization (WHO) as a neglected tropical disease, HAT is a protozoan parasitic infection borne by over 30 species of tsetse fly and is difficult to detect and fatal if left untreated. We develop and analyze a general temperature-dependent non-autonomus ODE model for the prevalence of the disease in several populations and fit it to West-African region for one species of vector, *Glossina tachinoides*. The model is extended to include an array of control strategies including trapping, insecticide treated cattle, the sterile insect technique, and active screening. The process of implementation, application, and optimization of each control strategy is analyzed numerically. In addition, the effects of climate change, external vector invasion, and barrier set-up are explored.

1. Introduction

Human African Trypanosomiasis (abbreviated HAT and commonly known as sleeping sickness) is an endemic public health threat to Sub-Saharan Africa. The disease is a major cause of rural underdevelopment in Sub-Saharan Africa as it mainly affects poor and remote rural regions[1]. Classified by the World Health Organization (WHO) as a neglected tropical disease[1], HAT is a protozoan parasitic infection borne by over 30 species of tsetse fly[1]. There are two morphologically identical forms of the infection: one caused by the protozoan *Trypanosoma brucei gambiense* and the other caused by *Trypanosoma brucei rhodesiense*[2]. *T. b. gambiense* is responsible for 97% of all HAT infections[3] and causes the chronic form of the disease, which can be asymptomatic for months or years[2]. In the first, or hemolymphatic, stage of the disease, various intermittent generic symptoms such as fever, headaches, fatigue, arthralgia, and pruritus can occur[15]. Other nonspecific signs include splenomegaly and enlarged cervical lymph

nodes. In the second, or neurological, stage of the disease, psychiatric, motor, sensory, and sleep abnormalities occur and the reversal of the wake-up cycle is common. Untreated patients ultimately die as a result of severe wasting, dysfunction of the immune system, or deep coma, often due to common bacterial infections such as pneumonia. The interval between the two stages is on the order of months or years[15]. The acute form of the disease caused by *T. b. rhodesiense* is much less prevalent but is also fatal if left untreated[2]. Illness due to *T. b. rhodesiense* usually occurs within 1 to 3 weeks after an infective bite and cannot be clinically distinguished from other tropical fevers such as malaria. Most deaths occur within 6 months from the beginning of the illness[15].

The clinical treatment of HAT is difficult; by the time the infection presents symptoms, few drugs are capable of fighting it, and those that exist are unpleasant and potentially life-threatening[4]. Due to its lack of symptoms, surveillance of HAT is difficult; only 16,000 cases are reported per annum[2]. Despite these figures, the WHO estimates that 55 million people are at risk and that, with proper surveillance, there would be 300,000-500,000 reported cases and 50,000 deaths per annum[5]. Furthermore, similar protozoa (notably *T. b. brucei*, *T. congolese*, and *T. vivax*) cause animal African trypanosomiasis (AAT), an infection that has a major impact on agricultural production in the region[6]. All trypanosomiases infect mammals exclusively[7].

Trypanosomes depend completely on the tsetse fly as a vector, with various lifestages taking place in both the mammalian host and the insect vector. Trypanosomes multiply in mammalian hosts, and are taken up when the fly bites the host[2]. Parasites mature in the fly, migrate to its salivary glands, and are transmitted back to the mammal via bite. The trypanosomes then multiply at the site of the bite for a few days before entering the blood stream and the lymphatic system of the mammalian host[15]. New parasites are then taken up into the tsetse fly when it takes a blood meal. Flies suffer no ill effects from carrying the infection[8]. Vertical transmission (from host to host or vector to vector) is not possible[7].

These thirty tsetse species are highly localized, so the specific vector of HAT varies greatly from region to region[7]. Tsetse species have different characteristics and vary in their vulnerability to infection[7], biting rate[8], life expectancy[8], and host preferences[8]. Furthermore, these characteristics vary significantly not just within each specific region and for each specific species but also with temperature and humidity[8]. These differences have a significant impact on the behavior of the disease. Hence, it is extremely dif-

ficult to develop a robust general mathematical model that would suitably describe the entire affected region.

Adding to this complexity is the fact that non-human mammals, both domestic and wild, can serve as a reservoir for trypanosomiases including HAT, even if these hosts are not directly affected by the disease[9]. Indeed, the prevalence of *T.b. gambiense*, which afflicts only humans, is in some areas much higher in non-human reservoirs than it is in the human population[7]. The significance of these reservoirs to the transmission of the disease has been subject of much debate[10], but recent evidence has suggested that animal populations do indeed serve as a meaningful reservoir for the disease, rather than just a dead-end outlet for the parasite[10]. While some research has been done on the importance of animal reservoirs, the exact role of domestic and wild mammals remains unclear[10].

Another important factor to consider when discussing HAT is the migration of both vectors and hosts. Because the tsetse fly requires very specific conditions for the deposition of pupae, it migrates extensively within its habitat. Although the flies tend to spend the majority of time resting in trees and local vegetation, a healthy adult tsetse fly travels up to several miles per day[8]. The existing research shows that the contact rates between the hosts and the vectors depend on the location[11] and on the displacement characteristics of the fly. Based on the ecological data available on the tsetse fly, the two most common depositories of pupae are human-maintained plantations and forested areas surrounding human settlements[8].

Managing the disease is often necessary and there exist a variety of control strategies for the control or eradication of the disease. The most commonly employed strategies rely on vector control, as managing the fly population often seems to be the most cost-effective and time-efficient option. Examples of tsetse control strategies include trapping, ground and aerial spraying, insecticide-treated cattle, and the sterile insect technique. Other, less environmentally sound approaches include game destruction and bush clearing. While these two approaches were used effectively in the past to both control and eradicate tsetse populations, such practices are now widely considered to be objectionable and unsustainable from an ecological perspective[17]. Other control strategies that do not directly control the vector population include human and animal screening and experimental vaccinations.

However, despite a wide range of possible control options, the flies remain widely distributed[19]. Part of the problem comes from the fact that HAT is a neglected disease and many African governments and large donors

have significantly reduced their financial commitment to tsetse control over the past years[19]. Hence, the operations are being run by local communities and inexperienced non-governmental organizations that often lack funding and expertise. Vale and Torr point out in their paper on user-friendly models of the costs and efficacy of tsetse control strategies[19] that the agencies controlling the disease often need help in selecting the appropriate control method and its best use. Since the ecology of the tsetse fly is well researched and the epidemiology of the disease is well understood, these issues can be effectively addressed through appropriate mathematical modeling of the disease behavior. There are several such models available to involved agencies, including user-friendly programs such as 'Tsetse Plan' and 'Tsetse Muse', that are freely available via the web. However, there is still a need for more sophisticated models, the authors further emphasize, as is suggested by the recent inception of the Pan-African Tsetse and Trypanosomiasis Eradication Campaign[19].

Development and validation of more sophisticated models is far from trivial. Human African Trypanosomiasis is quite difficult to detect in humans[18] and animals and detection efforts are often severely limited by the amount of resources available to the attendant agencies. The scarcity of screening data and the relatively low efficiency of the screening process itself make the validation of prevalence rates much more difficult[7]. Data on overall prevalence rates are infrequently collected at best. Furthermore, the data that does exist is typically collected at a single point in time and does not provide any valuable insight on the prevalence trends over longer periods of time. Consequently, it is no surprise that the true prevalence rates of the infection in humans, animals, and flies are largely unknown. Rough estimates used in the past literature place the prevalence in humans around five to ten percent, animal prevalence rates near twenty to thirty percent and vector prevalence under three percent[7]. To add to the complexity of the issue, the estimates of fly populations in the region are also highly approximate. In the majority of cases the data on the total fly population within a given region is based on the so-called "apparent density," an extrapolation of trapping data. However, apparent density data varies widely and is confounded by trap location, trap efficiency, temperature and humidity during the trapping period, vector migration, and by the relative proportion of hungry flies within the region.

As a result of these challenges, the majority of mathematical models of HAT tend to be broad in their structure and general in their conclusions. One of the first general models of HAT prevalence, which has since

been established as the foundational model on the topic, was developed by Rogers[7]. The model is based on a single-host malaria ordinary differential equation model developed by Aron & May and extended to two vertebrate host species in order to account for human and animal reservoirs. The model is fundamental in that it provided a concise summary of the existing epidemiological and ecological research and applied the findings to a hypothetical mathematical example of a typical West African village. HAT transmission rates are assumed to be determined by the estimated biting rates, the proportion of infected vectors and hosts, the proportion of bites resulting in transmission, and the ratio of vectors to hosts[4]. For the sake of simplicity, a few simplifying assumptions are made: the populations of vectors and hosts are considered to be constant, no migration of the vectors and/or hosts is assumed, and the parameter values are based on crude averages. Due to its general applicability and lack of sophisticated assumptions, this model serves as an ideal starting point for more intricate mathematical experiments. In our research, we incorporated and extended some of these ideas, e.g. in choosing the factors which determine transmission rates or the role of the animal reservoir.

A more intricate mathematical model was developed by Chalvet-Monfray et al[11]. The authors accounted for the spatial heterogeneity and migrations of the hosts and the vectors by developing a compartmental model that assumed vector and host migration between two patches. The two patches, namely "the village" where people reside and "the plantation" where people work, enabled the authors to account for the spatial differences in contact rates between the vectors and the hosts. The literature presented by the authors suggests that the contact rates between the vectors and humans in the village, where the domestic animals are the host of choice, are much lower than the contact rates on the plantation, where the humans serve as the vectors' primary host. These differences in the contact rates are important as they lead to significantly different disease behavior in the respective patches. Within each patch, the authors assume perfect mixing of both the vectors and hosts, incorporating an assumption that intra-patch dynamics are fast compared to the dynamics of the disease itself. While the results of the model are credible and provide some meaningful analysis, there are several simplifications made throughout the analysis. The paper does not account for an animal reservoir, which is thought to play a significant role in the dynamics of the disease[10]. In addition, while the model does account for human migration, it assumes that this migration is homogeneous within the human population. Nevertheless,

despite these shortcomings, the model provides a novel approach to the spatial heterogeneity problem which effectively simplifies and accounts for this complex issue. In our paper we employ the general approach designed by the authors, building on the simplicity and ingenuity of the two-patch compartmental model while also addressing the previously identified shortcomings.

In order to address these shortcomings, we incorporate the recent findings by Funk et al[10], who through the use of the next generation approach provide one of the first estimates of the disease's basic reproduction number based on actual field data. The authors provide convincing argument for the necessary inclusion of the animal reservoir when modeling *gambiense* Human African Trypanosomiasis[10]. In fact, after analyzing independent transmission cycles, the authors conclude that the presence of the animal reservoir is necessary for the existence of the disease. In addition, the authors also point out that control strategies which target only humans are insufficient, a finding consistent with the results of our own research.

Moreover, recognizing the importance of climate on the overall dynamics of the system, we dedicate a significant amount of effort on developing a suitable and proper model for the local temperature behavior that can be easily generalized to any specific region. Relying on the fact that thermodynamical state of the atmosphere can effectively be described in terms of temperature[12], we base our climate submodel on the research presented by Benth et al[12], in which the authors propose a spatial-temporal autoregressive stochastic model for daily average temperature data with seasonally dependent variance of the residuals. This model is especially useful, as it is quite flexible in apprehending the schematic features of temperature data, as well as being easily analytically tractable[12]. Due to its unique configuration, the model can be easily decomposed into its constituent parts in order to isolate and analyze the impacts of seasonality, average trend, mean reversion, and seasonal variance. Although the model was originally developed for the purposes of derivatives pricing, it can easily be extended for inclusion in a biological model.

The development and analysis of novel mathematical models are crucial for the further understanding of the disease's behavior. While developing a model that overcomes the discussed shortcomings and incorporates the nuances of the disease is one of the priorities of this paper, we believe that the main purpose of such models is to provide analytical insight to the control of the disease. In exploring the questions of control and eradication we rely on the research introduced by a variety of authors who have explored

the applicability of trapping (Hargrove, 2003)[16], sterile insect technique (Vale et al, 2005, Dame et al, 1967)[19,23], live-bait technique (Bouyer et al, 2007)[13], and screening (Robays et al, 2004, Chappuis et al, 2005)[18,15]. While the literature on control strategies is too extensive for a more detailed review and would distract away from the primary purpose of the paper, we elaborate on the relevant findings in the second part of our paper.

For the purposes of the thesis and the sake of transparency, we'd like to conclude our literature review by briefly focusing attention on the prior research done by the authors. Nejc Zupan started working on mathematical investigation of Human African Trypanosomiasis with another student, Tom Madsen, two years ago in a class on advanced calculus in biology and medicine (MATH 027) taught by Professor Dorothy Wallace. Madsen, Wallace, and Zupan continued working on the research initiated in that class and published a paper on seasonal fluctuation in tsetse fly populations and HAT prevalence rates. The published findings were also presented at BIOMAT 12th International Symposium on Mathematical and Computational Biology. The research presented at the symposium focused on the impact of non-constant temperature on the dynamics of the disease. It presented and analyzed a relatively simple version of a non-autonomous temperature-dependent fly population model coupled with a version of Rogers' epidemiology model. Madsen and Zupan continued the work on the topic in a computer science class on numerical and computational tools for applied sciences (COSC 070), where a first attempt was made to address the issue of controlling and eradicating the disease and a simple user-friendly modeling program was developed. Madsen and Zupan continued to present and discuss their research at 2013 NIMBioS Undergraduate Research Conference at the Interface of Biology and Mathematics. Finally, in their seminar class in applied mathematics (MATH 076) Birnbaum, Cho, Madsen, and Zupan developed a simple autonomous constant-temperature ODE model to investigate the importance of patch migrations and animal reservoir. However, despite the substantial amount of research done on the topic over the past two years, this thesis builds on previous work significantly - revising former findings, building a more complex and sophisticated model, meticulously incorporating the impact of control strategies, and extensively analyzing a wide array of contemporary issues not yet addressed by the existing literature.

It is worth pointing out that existing research on the topic indeed provides us with some very important conclusions that are crucial to furthering our understanding of the disease, such as the relevance of animal reser-

voir and the impact of vector and host migrations. Due to the modeling difficulties discussed above, however, the existing research is very limited in its applicability to specific scenarios. The purpose of this paper is to overcome these difficulties by synthesizing the valuable insights provided by pre-existing research and work done on the topic and to produce a comprehensive temperature-dependent non-autonomous model that can be applied to a variety of specific scenarios. The authors believe that the usefulness of such a model is wide-ranging, as it will help the researchers thoroughly understand the behavior of the disease for different conditions and circumstances without necessarily performing the capital-intensive and time-consuming epidemiological research. Furthermore, the authors use the model to explore the sensitivity of the disease to temperature and to study efficiency, time-effectiveness, and applicability of the various existing control strategies. In doing so, the authors hope to provide meaningful insight and direct applicability to researchers working to control this manageable yet neglected disease in the world's poorest regions.

The remainder of the paper is organized as follows: In Section 2, we develop the three submodels (vector population, prevalence, and temperature), and examine the behavior of the resultant overall model. In Section 3, we implement and examine four control strategies, developing optimal implementations of each. In Section 4, we'll discuss our results and consider possible directions for future work.

2. The Model

Our model describes the population dynamics of four groups of tsetse fly (pupae, tenerals, female adults, and male adults) and the prevalence dynamics of four hosts (workers, non-workers, domestic animals, and wild animals) and one vector population (tsetse fly).

The model furthermore assumes that part of several populations (namely workers, wild animals, and vectors) are split between the two patches: the village and the plantation. Spatial dynamics play an important role in the behavior of the disease[10]. In order to account for this dynamic, migration of populations between the village and the plantation is incorporated into the model. The two specific patches chosen are of significant importance for the insect population since they are the two most common depositories of pupae[8]. Furthermore, the two patches chosen also represent the two most common feeding sites for the vectors[8].

Migrations of both vectors and hosts between the patches are rapid

when compared to intra-patch dynamics of Human African Trypanosomiasis. This assumption is valid since the workers and vectors are assumed to travel between the patches on a daily basis[118]. Furthermore, according to the existing literature, the migrations between the patches are fast when compared to the spread of the disease[11]. This assumption allows for the incorporation of homogenization of the actively infected migrating populations across the patches. In other words, there is no meaningful difference between the prevalence of infection of any population in the village and in the plantation. The migrating populations (workers, wild animals, and vectors) are split between the two patches by a constant ratio. We further assume that at any given point in time a fixed proportion of each migrating population is in the village, while the remaining proportion is on the plantation. This is equivalent to assuming that each host/vector spends a certain proportion of time in the village and a corresponding proportion on the plantation. A spatially heterogeneous environment is assumed. A compartmental scheme of the entire model is depicted on the next page. Next, each of the submodels is introduced and discussed in detail. In addition, the adopted model for temperature is presented and analyzed at the end of the section.

2.1. *Insect Population Model*

As mentioned in the introduction, the submodel for insect population builds on the insect population submodel presented in the paper published by the authors in 2012[25]. That model is refined and thoroughly revised and we fully describe the amended version first presented in 2012 in this section of the paper.

A species of tsetse that lends itself to mathematical modeling is *Glossina tachinoides*, found in west and central Africa[8]. *G. tachinoides* is a member of *palpalis* group and is one of the major vectors of HAT[7]. It is the most northerly of the tsetses in west and central Africa and it is best suited to live in humid areas such as rainforests, swamps, and gallery forests[8]. Like most tsetse species, *G. tachinoides* is only susceptible to *T. brucei* infection during its teneral stage. That is, *G. tachinoides* becomes infected at their first blood meal or it does not got infected at all[26]. The life span of the fly, the durations of the pupal period and the length of the feeding cycle depend on temperature and humidity[8]. Populations of *G. tachinoides* near human settlements tend to prefer pigs as their source of blood meals, with cattle and humans as the next most popular options[24]. Hence, the

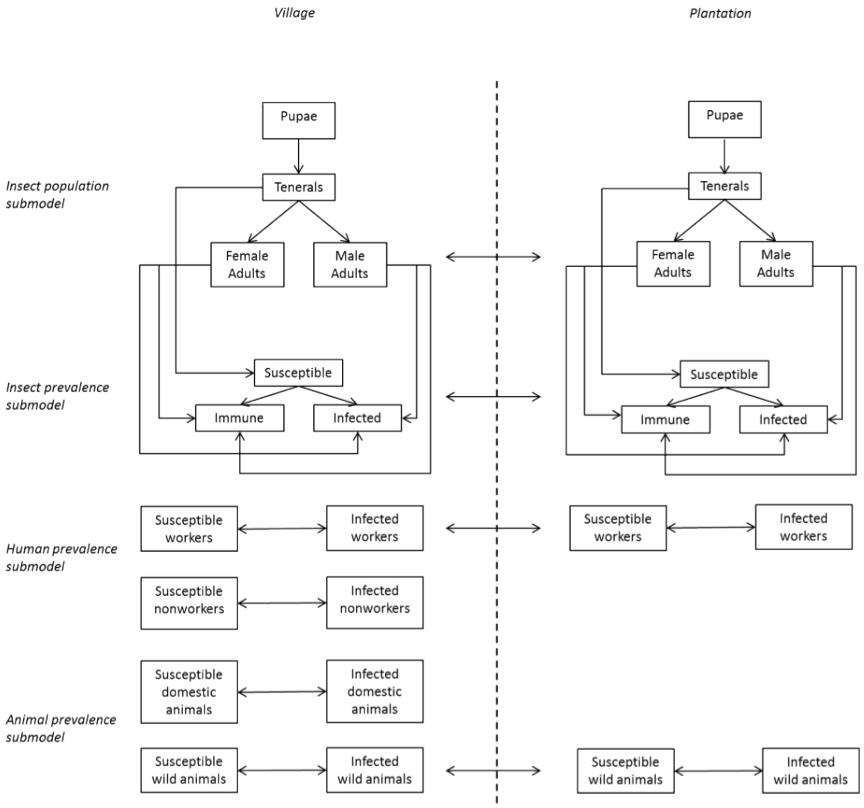

Figure 1. The compartmental scheme of the model. As explained on the previous page, intra-patch migration dynamics are fast compared to the dynamics of the disease. For the sake of transparency the detailed description of forces of infection and corresponding loss terms are ignored in the figure. The model is described by the set of differential equations (1)-(10) introduced on the following pages.

inclusion of animal hosts, both domestic and wild, is supported by the existing literature.

The life cycle of tsetse is complicated and rather unique[8]. While some literature suggests that adult females mate only once during their lifetime, entomology research conducted by Dame et al[23] coupled with respective literature review on the topic provides strong evidence for multiple mating of females. During the mating process, the adult male deposits a large ball of sperm directly into the uterus of the female, which travels into the spermathecae. The sperm remains active for the rest of the female's life.

Nevertheless, due to multiple mating of both males and females, part of the deposited sperm gets replaced by the sperm of the next male. While this nuance is irrelevant for a full population of fertile males, it becomes highly significant if sterile males are introduced into the ecosystem. We address this concern later in the paper during our discussion of sterile insect control technique. The female incubates one egg at a time. The egg passes into the uterus, where it is immediately fertilized. The egg spends four days developing into a larva, and about five days in a combination of three larval stages. About nine days after the egg passes into her uterus, the female deposits the fully-grown larva from her uterus into a patch of loose, protected soil, where it quickly develops a hard, dark shell, and becomes a pupa. The pupal period can last from about twenty to forty days, depending on the species, soil, humidity, and temperature[8]. At the end of the period, the shell breaks and a small fly emerges.

The time between hatching and the fly's first meal is known as the teneral stage[7]. The first meal is very important as this food is used to develop the flight muscles in the thorax, which are undeveloped at emergence[8]. Flies are vulnerable to infection by *T. brucei* in this weak state, and develop immunity after their first blood meal[7]. After the teneral stage, the flies enter the adult stage. After mating, adult females give birth to a single larva approximately every nine to ten days for the remainder of their lives. Males live about three weeks. Females usually live longer, although their life expectancy varies greatly between different species and is very sensitive to atmospheric temperature[8].

While teneral flies are rather dormant and rest up to a few days before their first meal[8], the adult flies tend to migrate daily, traveling up to several miles. Such migrations play a vital role in the dynamics of the fly population and the disease.

2.1.1. *Equations and Parameter Values*

We assume that every adult female fly mates successfully, independent of the male population. We base this assumption on the fact that female and male fly populations both mate multiple times and that the sperm deposited by a single male is capable of lasting throughout the lifetime of the female fly.

We furthermore assume that the temperature is non-constant, which makes our model non-autonomous. The effect of temperature on the parameters within the model, however, is assumed to be linear. We describe

each temperature-dependent parameter with a temperature-dependent linear function in order to crudely match the parameter ranges to the existing epidemiological data. This is a significant modification from the previous range-dependent estimation and it follows the existing literature more closely. Furthermore, this assumption allows us to generalize the model to any set of temperature data without the need to change the parameter values of the model.

The majority of the population models rely on a carrying capacity assumption to bound population growth. However, considering the life cycle of the tsetse fly, it is difficult to imagine what would impose such a bound. Fly populations are observed to vary widely with respect to a variety of factors (such as temperature, humidity, time of the day, etc.)[27,28,29] and there appear to be plenty of mammals to provide blood meals. Furthermore, the production of pupae is so small that no constraint seems relevant there. Therefore we do not assume any *a priori* bound on fly populations. Instead, we focus on the role of temperature as a controlling factor of vector growth and decay.

As pointed out in the introduction, the vector migrations between the patches are assumed to be rapid relative to intra-patch dynamics and spread of the disease. Hence, the fly population submodel describes homogeneous compartments that are spread between the two patches at a constant proportion.

Equations (1) - (4) below fully describe the vector population submodel. The four populations are represented algebraically as follows: P for pupae, R for teneral, F for female, and M for male.

The rate of change of pupae is determined by the rate of total population deposition less the rate of pupae maturation and the pupal death rate.

$$P' = FI^{-1} - P(Q_1 + Q_2T)^{-1} - VP \tag{1}$$

The rate of change of teneral population is determined by the rate of pupae maturation into tenerals less the rate of maturation of tenerals into adults (feeding rate) and the death rate.

$$R' = P(Q_1 + Q_2T)^{-1} - R(C_1 + C_2T)^{-1} - R(H_1 + H_2T)^{-1} \tag{2}$$

The rate of change of adult female population is determined by the rate of maturation of tenerals into female adults less the death rate.

$$F' = \frac{1}{2}R(C_1 + C_2T)^{-1} - F(S_1 + S_2T)^{-1} \tag{3}$$

The rate of change of adult female population is determined by the rate of maturation of tenerals into male adults less the death rate.

$$M' = \frac{1}{2}R(C_1 + C_2T)^{-1} - M(N_1 + N_2T)^{-1} \tag{4}$$

The values for all the parameters, variables, and initial conditions used in the equations (1) - (4) are described and summarized in Table 1 below. Table 1 provides an effective description of the parameters used in the insect population equations, gives default values for further numerical experiments and sources the research on which the estimates are based.

Table 1. Parameters and Variables: Vector Population Submodel

Notation	Value	Units	Description	Source
F	variable	number	female adult fly population, initially 3000	-
I	9	days	duration of larval period	[8]
M	variable	number	male adult fly population, initially 2000	-
P	variable	number	pupal population, initially 5000	-
R	variable	number	teneral fly population, initially 1000	-
T	variable	Celsius	temperature, varies with time	
V	0.04	-	average pupal death rate	[8]
C_1	0.25	days	Temperature adjusted average duration of fly feeding cycle - intercept	[8]
C_2	0.125	days^{-1}	Temperature adjusted average duration of fly feeding cycle - slope	[8]
H_1	11.2	days	Temperature adjusted death rate of tenerals - intercept	[8]
H_2	-0.13	days^{-1}	Temperature adjusted death rate of tenerals - slope	[8]
N_1	86.25	days	Temperature adjusted male life expectancy - intercept	[8]
N_2	1.875	days^{-1}	Temperature adjusted male life expectancy - slope	[8]
Q_1	68.36	days	Temperature adjusted duration of pupal period - intercept	[8]
Q_2	-1.07	days^{-1}	Temperature adjusted duration of pupal period - slope	[8]
S_1	172.5	days	Temperature adjusted female life expectancy - intercept	[8]
S_2	-3.75	days^{-1}	Temperature adjusted female life expectancy - slope	[8]

2.1.2. *Explanation of Equations and Parameters*

Pupa population

The daily rate of pupae deposited is a function of the total number of adult female flies in the ecosystem and the rate at which females are depositing pupae. The literature suggests that, on average, an healthy adult female deposits one pupae every ten days and has a larval period of about nine days[8]. Furthermore, Rogers advocates that tsetse flies breed continuously and consistently and not in cycles[7], meaning that the rate of deposition of pupae by female flies is not directly dependent on external factors such as for example temperature. Hence, for the purposes of our model, we are safe to assume that on any given day, the total number of pupae deposited into the ecosystem is precisely one-ninth the number of adult female flies. As pointed out in our initial research, using a ten day estimate for the length of the larval period does not significantly alter any of the results.

Once the pupae are deposited, they slowly mature until they eventually

emerge into tenerals. The rate of such emergence depends on the climate conditions, especially on atmospheric temperature. For our species, on average, the length of such period is 25-30 days[87]. However, entomological research conducted by WHO suggests that the length of the so-called pupal period is longer than average during the periods of lower temperatures and shorter during the periods of higher temperatures[8]. According to the literature, the pupal period ranges between twenty-three days at the average temperature of 33 degrees Celsius and thirty-eight days at the average temperature of 19 degrees Celsius[8]. To model such behavior, we assumed that the relationship between the average rate of daily emergence of pupae and daily temperature is linear. While such assumption is indeed an estimate, there is no entomological research in existence that would provide a better approximation. Hence, for the sake of simplicity and in order to avoid making unnecessary and unfounded assumptions, linearity is assumed. This is a slight revision from the previous research done by the authors where the temperature served as a correction factor, mainly to address our lack of data collected and research done on the local temperature behavior at that point. As our temperature data and model is now more sophisticated and researched, we now feel confident enough to remove the unnecessary additional restriction and rely completely on the temperature to serve as an implicit boundary and accelerator to growth. Hence, using our pupal period range as the source of data we obtain a first degree polynomial approximation for the relationship between the temperature and the pupal period and used the estimate to approximate the emergence of flies from pupae into tenerals. Due to lack of available data, the method yields highly approximate results. However, the negative relationship between the duration of the pupal period and the average temperature is established and addressed within the scope of the existing research.

Because the pupae can die in many ways (parasites, predators, flooding, and dehydration are all established causes of pupal death[8]) and because the precise impact of these threats is not well known, the daily death rate of pupae is difficult to estimate. Furthermore, some data even suggests that pupal death rate might be correlated with temperature, beyond the impact of the temperature extremes[8]. Entomological research conducted by the WHO yields inconclusive results as at the end of four-month long rainy season, when the pupae was collected for the count, about half of pupae collected were found dead. At other times, however, all pupae were found to give rise to adult flies[8]. Assuming a fixed rate of pupae deposition, we estimate that about eight percent of pupae would need to die with

each generation (about ten generations in four months) in order for the researchers to find as many dead pupae as living ones at the end of a four month long rainy season. Coupling this estimate with the rest of the entomological research that found no dead pupae, we decide to fix our estimate for pupae death at four percent. Again, while this estimate tries to make the best out of the data available, it is still highly approximate and there is need for further field research on the topic.

Teneral population

Tenerals are the flies that have successfully emerged from pupae and have not yet taken their first blood meal. The teneral stage is a very delicate stage of the flys life cycle as the flies are atypically weak before they take their first meal, sometimes needing to rest up to a few days before gathering the strength to fly to the nearest available host. Tenerals emerge from pupae at the rate that was discussed in the previous paragraph - the pupae loss term due to emergence is identical to teneral gain term. Teneral loss term is dependent on the properties of the fly's feeding cycle as the teneral emerges into an adult fly immediately after its first blood meal. The literature suggests that the frequency of biting and consequently the rate of emergence of tenerals into adults is temperature dependent[8]. Low temperatures increase the amount of time that the flies can last without a blood meal and high temperatures tend to have the opposite effect[8]. While there is no data available for our specific species, the existing research indicates about a 20% fluctuation in the duration of the feeding cycle. Hence, coupling this estimate with the average estimate for the length of the feeding cycle (provided by Rogers) of four days[7], we again approximate the relationship between emergence into adults and temperature with a first degree polynomial. Following the same procedure as before, we obtain an estimate for the relationship between temperature and teneral death rate, since as mentioned previously, tenerals are especially prone to external influences and climate plays an important role in determining their survival rate.

Female adult population

Adult fly population is a function of two terms, the emergence of tenerals into adults and the death rate. The emergence of tenerals is, as discussed above, dependent on temperature and varies significantly with time. For the purposes of our model, we assume that half of the tenerals emerged develop into female adult flies, while the other half develops into males.

Much like for tenerals, the death rate of adult females is believed to be temperature dependent as well. In our previous research, we made an

assumption that the relationship between temperature and female adults death rate is quadratic in its nature. After a careful review of the literature, we now change this assumption and instead adopt linearity. Following our intuition from the previous paragraphs, flies indeed tend to live longer during low temperatures and shorter during high temperatures[8]. There is however, field evidence for the quadratic relationship between temperature and fly activity as flies tend to be the most active when the temperature is in intermediate range[8]. Hence, based on further research, we revise the female adult death term and approximate it with a first degree polynomial.

Male adult population

The dynamics of the adult male population are quite analogous to the dynamics of the female adults. The only significant difference is that the life expectancy of the male adults is much shorter[8]. In our previous research, we made an assumption that male adult death rate is fixed with time and not temperature-dependent. In light of further research, we now revise this assumption and assume a linear relationship between temperature and death rate[8]. Hence, we change the dynamic of the system significantly and hopefully enhance the ability of the model to mimic entomological reality.

2.2. *Prevalence Submodels*

In the previous section we developed and described an intricate insect population submodel for *G. tachinoides*. In this section we perform a similar task as we introduce and develop five differential equations describing HAT prevalence rates for one vector and four hosts (workers, non-workers, wild animals, and domestic animals) for a medium-sized West African village that is a few miles away from a proportionately-sized plantation. Hence, our prevalence submodels strive to build on the previous research and findings in order to construct a broadly useful model.

In order to address the importance of vector migration and to investigate the implications that it has on the disease dynamic we decide to address spatial heterogeneity by splitting the system into two patches; village and plantation. The choice of patches is deliberate as the existing field research shows that tsetse flies indeed congregate around human-populated areas with villages and plantations mentioned as principal examples[8]. Furthermore, this split has been introduced and defended by Chalvet-Monfray et al. who further emphasized the inclusion of patches due to their impact on the disease dynamic[11]. Nevertheless, our model builds significantly on previous two-patch models by adopting a more realistic assumption about migrating

human subgroups (workers vs. nonworkers). Additionally, incorporating research presented by Funk et. al, we also assume the existence of animal reservoir that is, just like the human population, split into a migrating and non-migrating subgroups (domestic animals vs. wild animals).

As mentioned previously, we assume that the intra-patch disease dynamics are fast in the sense that the migrating groups (vectors, workers, and wild animals) migrate between the patches fast enough to not build up any significant difference in their prevalence between patches. We find this assumption reasonable, since intra-patch migrations take less than a day, while the dynamics of the disease occur on the order of weeks and months. We also assume that the prevalence rates for the migrating groups between the two patches are the same (perfect mixing). Again this assumption is reasonable as the migrating groups tend to migrate not just fast, but also quite often (on a daily basis). These same assumptions are also adopted by Chalvet-Monfray et al[11]. Furthermore, the sensitivity analysis done by Birnbaum, Cho, Madsen & Zupan on the importance of rapid and frequent migration showed that the change in the level of mixing does not change the behavior of the disease significantly.

2.2.1. *Equations and Parameter Values*

In this section we present the equations along with the correspondent parameter values for all the prevalence submodels. Equations (5) - (9) below fully describe the prevalence submodels for the vectors (Y), workers (W), non-workers (N), wild animals (A_W), and domestic animals (A_D).

Vector prevalence gain is a function of host-specific biting rate, probability of an infection from an infected bite, proportion of infected hosts and proportion of susceptible vectors. Vector prevalence loss is a function of adult male female death rate. The overall prevalence is a function of both, village and plantation dynamics.

$$Y' = (C_1 + C_2T)^{-1}\left(\frac{R}{R+M+F}\right)\left(h_v\left(\frac{ZWm_W + Nm_N}{Zm_W + m_N}\right) + w_vUA_W + dA_D + h_p(1-Z)W + \ldots\right.$$
$$\left. \ldots + w_pA_W(1-U)\right)c - Y\frac{(S_1 + S_2T)^{-1}F + (N_1 + N_2T)^{-1}M}{M+F} \qquad (5)$$

Workers prevalence gain is a function of the length of a feeding cycle, probability of a bite on the worker, percent of susceptible workers, current vector prevalence, and a number of vectors and hosts in the system for each respective patch. Workers prevalence loss is determined either through

recovery or death. The overall prevalence is a function of both, village and plantation dynamics.

$$\begin{aligned} W' =&(C_1 + C_2T)^{-1}h_vZ(1 - (W(1 + \frac{r_h}{i_h} + \frac{r_h}{v_h})))Yb_h\frac{M+F}{Zm_W + m_N} + ... \\ &... + (C_1 + C_2T)^{-1}h_p(1 - Z)(1 - (W(1 + \frac{r_h}{i_h} + \frac{r_h}{v_h})))Yb_h\frac{M+F}{(1-Z)m_W + m_N} - ... \\ &... - r_hW \end{aligned} \quad (6)$$

Non-workers prevalence equation is analogous to the one for the prevalence of workers, except that it only addresses a single patch, since non-workers don't migrate by assumption.

$$N' = (C_1 + C_2T)^{-1}h_v(1 - (N(1 + \frac{r_h}{i_h} + \frac{r_h}{v_h})))Yb_h\frac{M+F}{Zm_W + m_N} - r_hN \quad (7)$$

Wild animal prevalence gain is a function of the length of a feeding cycle, probability of animal biting, percent of susceptible wild animal population, current vector prevalence, and the number of vectors and hosts in the system for each respective patch. Wild animal prevalence loss is determined either through recovery or death.

$$\begin{aligned} A'_W =&(C_1 + C_2T)^{-1}w_vU(1 - (A_W(1 + \frac{r_w}{i_w} + \frac{r_w}{v_w})))Yb_w\frac{M+F}{UA_Wm_A} + ... \\ &... + (C_1 + C_2T)^{-1}w_p(1 - U)(1 - (A_W(1 + \frac{r_w}{i_w} + \frac{r_w}{v_w})))Yb_w\frac{M+F}{(1-U)A_Wm_A} - ... \\ &... - r_wA_W \end{aligned} \quad (8)$$

The domestic animals prevalence equation is analogous to the one for the prevalence of wild animals, except that it only addresses one patch dynamic since domestic animals don't migrate by assumption.

$$A'_D = (C_1 + C_2T)^{-1}dU(1 - (A_D(1 + \frac{r_d}{i_d} + \frac{r_d}{v_d})))Yb_d\frac{M+F}{A_Dm_D} - r_dA_W \quad (9)$$

The values for all the parameters, variables, and initial conditions used in the equations (5) - (9) are described and summarized in Figure 2 below. Figure 2 provides an effective description of the parameters used in all the prevalence equations, gives default values for further numerical experiments and lists the sources on which the estimates are based.

Table 2. Parameters and Variables: Prevalence Submodel

Notation	Value	Units	Description	Source
Y	variable	-	prevalence of infection in vectors	-
W	variable	-	prevalence of infection in workers	-
N	variable	-	prevalence of infection in non-workers	-
A_W	variable	-	prevalence of infection in wild animals	-
A_D	variable	-	prevalence of infection in domestic animals	-
h_v	0.2	-	Probability of a bite on a human in the village	10
h_p	0.4	-	Probability of a bite on a human in the plantation	10
w_v	0.3	-	Probability of a bite on a wild animal in the village	10
w_p	0.6	-	Probability of a bite on a wild animal in the plantation	10
d	0.5	-	Probability of a bite on a domestic animal	10
c	0.01	-	Probability of a first blood meal leading to an infection for tenerals	7
r_h	$\frac{1}{70}$	days^{-1}	inverse duration of infection in humans	7
i_h	$\frac{1}{12}$	days^{-1}	inverse duration of incubation in humans	7
v_h	$\frac{1}{50}$	days^{-1}	inverse duration of immunity in humans	7
r_w	$\frac{1}{60}$	days^{-1}	inverse duration of infection in wild animals	-
i_w	$\frac{1}{12}$	days^{-1}	inverse duration of incubation in wild animals	-
v_w	$\frac{1}{50}$	days^{-1}	inverse duration of immunity in wild animals	-
r_d	$\frac{1}{100}$	days^{-1}	inverse duration of infection in domestic animals	-
i_d	$\frac{1}{12}$	days^{-1}	inverse duration of incubation in domestic animals	-
v_d	$\frac{1}{50}$	days^{-1}	inverse duration of immunity in domestic animals	-
m_W	100	-	size of working human population	-
m_N	200	-	size of non-working human population	-
m_A	500	-	size of wild animal population	-
m_D	50	-	size of domestic animal population	-
b_h	0.62	-	Probability of an infected bite leading to an infection in humans	7
b_w	0.1	-	Probability of an infected bite leading to an infection in wild animals	10
b_d	0.1	-	Probability of an infected bite leading to an infection in domestic animals	10
Z	0.7	-	Constant proportion of workers in village	-
U	0.5	-	Constant proportion of wild animals in village	-

2.2.2. *Explanation of Equations and Parameters*

Vector prevalence

As mentioned in the explanation of the fly population submodel, the biting rate is temperature-dependent and is modeled precisely as it was

described in the previous subsection. We assume that only teneral flies can get infected. After an emerged fly takes its first blood meal, it either becomes infected or it becomes immune for the rest of its life cycle[8]. This assumption is supported by the existing literature and is based on the intuition that a teneral fly has a much weaker immune system and is hence not able to fight the possible infection. There are instances where especially weak and starved adult flies can, for the same reasons, adopt an infection, but we decide to ignore such outliers since there is no data available on their behavior.

Host-specific biting rate depends on the biting preferences of the specific fly and on the availability of the hosts. For our species, *Glossina tachinoides*, we assume that vectors prefer domestic animals over wild animals and wild animals over humans (the specific estimates are given in Table 2). Our estimates are supported by the literature and are based on the entomological research estimates provided by Simmo et al (Simmo et al, 2008) and summarized by Funk et al (Funk et al, 2013). It is worth pointing out, however, that such estimates can vary with the region and with the village structure and need to be interpreted carefully. The availability of the hosts is assumed to be perfect in aggregate, suggesting that a fly will always have an available host of each subcategory within its daily displacement radius. Since a fly can move up to several miles within one day[8], such assumption is reasonable.

The probability of a first bloodmeal giving rise to a mature infection in a teneral (parameter c) is hard to estimate and to the best of our knowledge there is no recent research that would provide field data for our specific trypanosoma and our specific vector species. Nevertheless, based on laboratory experiments performed on other species for the same trypanosoma[7] we estimate that the value must be somewhere in the range from one to ten percent. In order to avoid overstating the impact of the disease we opt for the lower range of the spectrum, setting the probability at one percent.

Since the state of infection or full immunity is established after a first blood meal, the infections are lost only at a death rate of the infected flies. (Infected flies never clear the infection.) Based on our research, we have no reason to believe that the infected flies have a different death rate than uninfected flies. Hence, we model our loss term as a temperature dependent death rate as described in the previous subsection.

Since we assume, for the reasons previously discussed, rapid and frequent vector migration between the two patches, the overall vector prevalence is the same throughout the region and does not vary between the

patches.

Human prevalence

We divide our human population into workers who migrate between the two patches and non-workers, who remain in the village. The length of the feeding cycle is a temperature-dependent parameter that determines the frequency of biting and has been discussed in detail previously. In our model we multiply its inverse by a probability of a bite on a worker (or non-worker) in order to obtain the daily number of bites for a single fly and for a single host. As suggested in Table 2, these biting probabilities depend on whether a person is located on the plantation or in the village. Since plantations have open space with fewer animals than a village, the workers that migrate to work experience biting much more frequently than non-workers. Hence, it should be no surprise to expect different prevalence rates between the workers and non-workers.

In order to arrive to the number of infected bites taken by a fly on a specific host, we need to multiply the number of overall bites with the overall prevalence rate for vectors and with the overall ratio of the host population that is susceptible to an infection. This will in turn allow us to calculate the number of infections raised in a specific host by a single fly as we multiply the expression with the probability of a random infected bite leading to an infection. Lastly, in order to adjust for the total number of vectors and hosts in the system and to arrive to the overall daily prevalence gain we need to multiply the final calculation by the ratio of vectors to hosts.

As indicated before, the workers and non-workers will leave the infected pool and enter the susceptible population by either recovering from the infection or, implicitly, since the human population is assumed to remain constant, by dying.

Animal prevalence

The submodel for animal prevalence is structurally quite similar to the submodel for human prevalence just described. Animal population is divided into two subgroups, wild animals and domestic animals, where the wild animals migrate rapidly and frequently between the two patches and the domestic animals remain fixed in the village. Much like the human prevalence, animal prevalence is also a function of the length of a feeding cycle, probability of an animal being bit, percent of susceptible animal population, current vector prevalence, and the number of vectors and hosts in the system for each respective patch.

Similarly to human prevalence submodel, we first multiply the inverse of the length of a feeding cycle by a probability of a bite on an animal in

order to obtain the daily number of bites for a single fly on a single host. The biting probabilities for animal subpopulations are crude estimates and depend on the region and on the type of the animal, as pigs, for example, tend to have a higher biting probability than sheep[10]. In our model we assume an average village with equally many wild and domestic animals distribution.

Following the same process described for human prevalence submodel, we arrive at the overall daily prevalence gains for the domestic and wild animals. Due to migration, the wild animal subpopulation dynamic is a slightly more complex than the domestic animal model, but follows the same underlying intuition.

Both domestic and wild animals will leave the infected pool and enter the susceptible population by either recovering from the infection or implicitly, by dying, since the population is assumed to remain constant.

2.3. *Temporal Stochastic Temperature Model*

The duration of almost every stage in the tsetse lifecycle is temperature-dependent[8]. Temperature is considered to be the most important characteristic of the thermodynamic state of the atmosphere, as it influences other atmospheric factors such as humidity, air pressure, and precipitation[12]. Hence, temperature helps us to understand and explain the impact of the atmosphere and its elements on the behavior of the tsetse fly. In fact, our previous research has shown that temperature plays a crucial role not just in its impact on the behavior of the tsetse fly, but also in its effect on the behavior of the disease[25]. Understanding the importance of the temperature, we decided to put extensive focus on the construction of a temperature model that will allow us to rigorously investigate the impact of the temperature variation on the behavior of the system. Relying on the spatial-temporal stochastic model with seasonal variance for daily average temperature data presented by Benth et al[12], we construct a comprehensive model that allows us to control for trend, seasonality, mean reversion, and seasonally dependent variance of the residuals. We present and introduce the model in this subsection.

We fit the suggested model to the average daily temperature data collected in Tillabri, Niger for the period from 1968-1980. This site was chosen deliberately, as it is in the center of the region in which our species of fly, *G. tachinoides*, is located. The model and the attendant MATLAB code, however, were designed generically to fit a model for any input data period

and for any region.

The original model presented by Benth et al.[12] extends the model to the spatial domain, which would allow us to control for region dependency. However, this property is dropped for the purposes of our analysis, as the behavior of the tsetse species is region-dependent[8] and our model is not sufficiently sophisticated to model this behavior. For regions that vary significantly in their natural characteristics (such as for example size, types of flora and fauna, and the type of soil), a vector population model needs to be amended accordingly. However, if the regions explored have similar characteristics, the temperature model can be easily extended to account for spatial dependency of temperature.

2.3.1. *Benth's Model, Amended*

We now present an amended version of the model presented by Benth et al[12]. For the original version and its applications, please refer to the original paper. In order to construct a spatiotemporal temperature model, we must first define the spatial-temporal Gaussian random field. For the sake of clarity, we keep the notation consistent with the model proposed by Benth et al.

$$\left\{Z(s,t) : s \in D \subset R^2, t \in \{0,\infty)\right\} \tag{10}$$

where s and t describe spatial and temporal coordinates, respectively[12]. Since our analysis we focus on one specific location (which is assumed to be small enough that temperature is uniform), our spatial domain only has one dimension and our model can be simply written as

$$Z(t) = \mu(t) + \varepsilon(t) \tag{11}$$

where $Z(t)$ is a time series temperature data (for the specific spatial location), $\mu(t)$ denotes the mean process, and $\varepsilon(t)$ denotes the residual process. The mean process can be further described as

$$\mu(t) = S(t) + \alpha(Z(t-1) - S(t-1)), \tag{12}$$

where

$$S(t) = l(t) + s(t). \tag{13}$$

Here $l(t)$ describes a linear trend and $s(t)$ describes the seasonality in daily average temperatures. The regression equations are as follows:

$$l(t) = a_0 + a_1 t \tag{14}$$

$$s(t) = b_1 + b_2 \cos(\frac{2\pi(t - b_3)}{365}). \tag{15}$$

Similarly, the residual process can be given as

$$\varepsilon(t) = \sigma(t)\epsilon(t) \tag{16}$$

Where $\sigma(t)$ describes a seasonally dependent standard deviation function and $\epsilon(t)$ is defined as a zero-mean temporally independent Gaussian random process with standard deviation equal to 0.1.

$$\sigma^2(t) = c_1 + \sum_{k=1}^{4} \left[c_{2k} \cos(\frac{2k\pi t}{365}) + c_{2k+1} \sin(\frac{(2k+1)\pi t}{365}) \right] \tag{17}$$

2.3.2. *Fitting the Model*

In order to fit the model to the described daily average temperature data, we follow a step-by-step process, analogous in structure to the process described by Benth et al, in order to methodically estimate, account for, and isolate each trend component contribution from the data. While this section describes the process we followed for sake of transparency, a MATLAB program was developed for easy reproduction of results for any daily average temperature data. The code is attached in an appendix.

First, we estimate the linear trend and subtract the linearity from the model. The linear trend in daily average temperature is estimated by running a simple linear regression and observing for statistically significant nonzero results. The obtained slope is approximately equal to $a_1 = -0.0002$ and the intercept is equal to $a_0 = 30.3223$. Our linear regression suggests a negative trend, which indicates a decrease in the local mean temperature over the period. The temperature data is in degrees Celsius. Our linear trend can be described as:

$$l(t) = 30.3223 - 0.0002t \tag{18}$$

Second, after subtracting for linearity, we focus on the analysis of the seasonal effects of the residuals. The residuals exhibit a clear seasonal pattern and we now estimate this trend by fitting the residual data using the nlinfit method in MatLab. We can then describe the seasonality trend as:

$$s(t) = -0.0212 - 2.9770\cos(\frac{2\pi(t+41.3777)}{365})(19) \tag{19}$$

Third, after subtracting for linearity and seasonality, we analyze the linear association between lagged observations and estimate the impact of mean-reversion on the obtained residuals. Using MATLAB, we apply an autoregressive model of order 1 (mean-reverting model) to obtain the coefficient value of $\alpha = 0.7979$. The AR(1) model developed relied on Burgs lattice-based method for computing the least-squares AR model.

Fourth, after subtracting for linearity, seasonality, and the impact of mean reversion, we focus on the analysis of the residuals, $\varepsilon(t)$. In order to account for seasonally-dependent variance, we first average the values of the squared residuals of the particular day for all of the years. Next we model the obtained values through truncated Fourier function fitting. The results for the parameters described in equation (17) are presented in Table 3.

2.3.3. *Fitted Model Equations and Parameters*

In this section we summarize the results of the model fitting process introduced and described in the previous subsections. Our final model has been fitted to the average daily temperature data collected in Tillabri, Niger for the period from 1968-1980 and is fully described by the following equation:

$$Z(t) = a_0 + a_1 t + b_1 + b_2 cos(\frac{2\pi(t-b_3)}{365}) + \alpha(Z(t-1) - S(t-1)) + \varepsilon(t) \tag{20}$$

where $\sigma(t)$ is defined as

$$\sigma^2(t) = c_1 + \sum_{k=1}^{4}\left[c_{2k}\cos(\frac{2k\pi t}{365}) + c_{2k+1}\sin(\frac{(2k+1)\pi t}{365})\right] \tag{21}$$

and $\epsilon(t)$ is a zero-mean temporally independent Gaussian random process with standard deviation of 0.1.

The values for all the parameters used in the two equations introduced above are summarized in Table 3 below, which provides an effective description of the parameters used in the model and gives region-specific values for further numerical experiments.

Table 3. Parameters: Temporal Stochastic Temperature Model

Notation	Value	Units	Description
a_0	30.3223	$\circ$Celsius	linear trend - intercept
a_1	-0.0002	$\frac{\circ\text{Celsius}}{\text{days}}$	linear trend - slope
b_1	-0.0212	$^\circ$Celsius	seasonal effect coefficient
b_2	-2.9770	$^\circ$Celsius	seasonal effect coefficient
b_3	-41.3777	days	seasonal effect coefficient
α	0.7979	-	mean reversion effect coefficient
c_1	-19.07	-	truncated Fourier series coefficient
c_2	-104.48	-	truncated Fourier series coefficient
c_3	199.27	-	truncated Fourier series coefficient
c_4	236.68	-	truncated Fourier series coefficient
c_5	-203.17	-	truncated Fourier series coefficient
c_6	-131.76	-	truncated Fourier series coefficient
c_7	63.18	-	truncated Fourier series coefficient
c_8	20.69	-	truncated Fourier series coefficient
c_9	-3.59	-	truncated Fourier series coefficient

2.4. *Full Model: Numerical Results*

We now present and discuss the numerical results of fully developed model described in this section. The model was developed and constructed in MATLAB using equations (1)-(4) and Table 1 for the insect population submodel, equations (5)-(9) and Table 2 for the prevalence submodels and equation (20) and Table 3 for the temperature submodel. In the plot presented below, the full model was run for a period of 1000 days.

In our previous paper (Madsen, Wallace & Zupan, 2012) we have shown analytically that temperature determines the stability or instability of the system and provides an example of a continuous switched system. In this paper, for the sake of brevity and focus, we choose to forego such analysis and instead rely on the findings established by the previous research and the numerical results yielded by this model. Indeed, as indicated in the

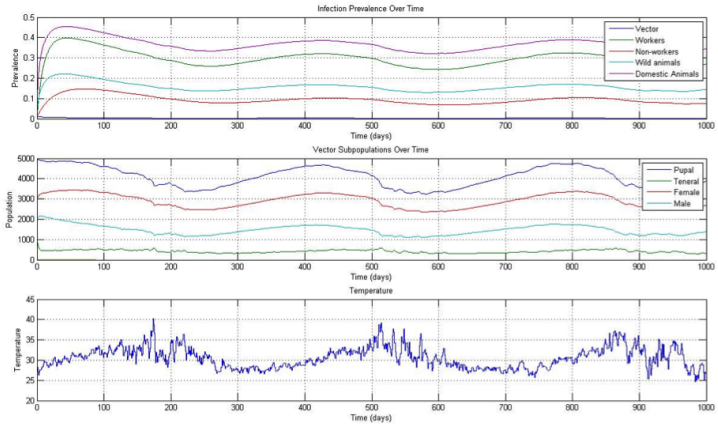

Figure 2. The numerical result for the full model that was run for 1000 days. The top graph shows the prevalence rates (percent of the total population infected) for vectors, workers, non-workers, wild animals, domestic animals, and vectors. The middle graph shows the populations for all four different stages of the insect life cycle (pupae, tenerals, female adults, and male adults). The bottom graph shows a temporal stochastic temperature curve with seasonal variance.

introduction and as the figure above demonstrates, temperature serves as an effective damper on the exponential growth or decay behavior of the insect population that is temporal and temperature-dependent. The fly population tends to slowly decrease during the period of the year in which the temperature is rising and slowly increase during the periods of climate cooling, which is consistent with entomological research[8]. Furthermore, the population levels for each stage (pupal, teneral, adult) tend to stay within reasonable ranges according to our data gathered for an average sized West African village[7].

Quite remarkably, the prevalence rates exhibited by the system are also within the range of what the existing research on the disease indicates[7,11,10]. Furthermore, the model clearly supports the established argument that argues for the inclusion of migration. The migrating portion of the human population, the workers, exhibit much higher prevalence rates than the rest of the human hosts, a direct consequence of different biting preferences between the two patches. Also, the oscillations in prevalence rates are not as large as the oscillations in the vector population, which is expected. The oscillations could become more frequent and larger if more aggressive medical practices that would return the infected portion of the population

back to the susceptible pool were assumed.

Unfortunately, field data on the behavior of insect population and prevalence rates is very scarce. Consequently it is hard to validate our model beyond the scope of reasonable range estimates provided by the literature. Screening is difficult, especially in vectors and wild animals. Furthermore, due to their constant vertical and horizontal migration, the insect population is very hard to determine with the use of conventional means such as trapping. However, as previously mentioned, the authors feel very confident about the results yielded by the model as the prevalence rates are consistent with the estimates suggested by the literature. The domestic animals have the highest prevalence rate, closely followed by the workers. Both prevalence rates are on the higher end of the spectrum, but still completely plausible[11]. The same is true for the other two hosts, wild animals and non-workers who are also exhibiting the behavior supported by the established research[7]. In addition, vector prevalence rates, while hard to determine in reality, fluctuate around the established values as well[7].

It is also worth noting the relationships and lags between the graphs presented in Figure 2. For instance, we notice a negative relationship between temperature and vector populations, which results in a small lag between the temperature curve's lowest point and the peak vector population, which is a consequence of the tsetse reproduction cycle. There also exists a lag between the vector population peak and the peaks in the prevalence rates, a consequence of the dynamics of the disease. The summation of these two lags in turn describes the impact of temperature on the the prevalence rate.

3. Analysis of Control Strategies

In this section we will further extend the model developed in the previous section and apply it to a variety of pressing questions that have arisen in topic literature. While we certainly will not answer all these questions, we will provide the reader with a numerical tool to further explore them. In order to motivate further research and contribute to the existing one, we will, however, address the most interesting and important queries within each topic. The topics included in our analysis include temperature, invasion and barriers, trapping, live baiting, sterile insect technique, and screening.

There are a few general assumptions that we will make throughout our analysis of the control strategies. We will assume that the controlled region (village and plantation) is being regulated for the possible vector invasion through either natural (ocean, dessert) or artificial (trapping, deforestation)

barriers. This assumption will allow us to focus solely on the effect of the specific control strategy and hold the impact of the external factors such as invasion at a negligible level. Although grand, such assumption is not unrealistic. In fact, effective barrier set-up reduces the probability of invasion down to 0.001[20] and effectively completely reduces the risk of re-invasion. In addition, we will analyze the impact of control strategies on the disease behavior in instances when invasion is not being regulated effectively at the end of the section.

When assessing the introductory effectiveness of each control strategy, we will assume realistic default values for the parameters that are based on our research on the topic. Nevertheless, our model does allow user a great deal of flexibility and the majority of the parameters can be easily adjusted for further research on the topic.

Due to great variance in prices with respect to an organization, scale, time of the year, quality of products, etc., we do not impose any cost function constraints on the overall system but rather explore the overall effectiveness of the control strategies with respect to optimization and time efficiency. We are aware that the cost often pre-determines the extent of a control operation and the model can be easily adjusted to account for the cost of the operation. Furthermore, a publicly expressed priority of several African governments, which are amongst the largest funders of the control projects, is to eliminate the tsetse and Trypanosomiasis problem in the shortest time possible[20]. Hence, for the sake of general applicability, we decide to avoid the incorporation of potentially misleading cost-related assumptions and instead focus on speed and effectiveness.

3.1. *Temperature*

Before we begin our analysis of control strategies, we choose to explore further the role of temperature on the disease system. The role and impact of temperature has been discussed and investigated extensively in the previous section of the paper. Hence, we utilize this portion of the paper merely to address a possible application of the model, namely the impact of global warming on the development of the disease. Because HAT is a disease that is very temperature-sensitive, the global climate change will change the behavior of the disease significantly, pushing it to either grow or decay at a much faster rate. In order to investigate the impact of such climate change on the overall behavior of the system we utilize our temporal stochastic temperature model introduced on the previous pages. This model allows

the user to isolate and model the impact of linearity, seasonality, or variance change on the system. For the purposes of our analysis, we merely focus on the linearity portion of the model since the recent research published suggests that the mean maximum temperatures display little or no warming[30]. Hence, we assume three different scenarios: no macro change, constant additional increase of 0.015 Celsius per year and constant additional decrease of 0.015 Celsius per year. This change is consistent with the recent trend, according to NASA, as the temperature has been rising at a rate of roughly 0.15-0.20 per decade since 1975. We will run both simulations for 10 years in order to allow for the impact of the trend to be visible. We present the impact on the prevalence rates in the figure below.

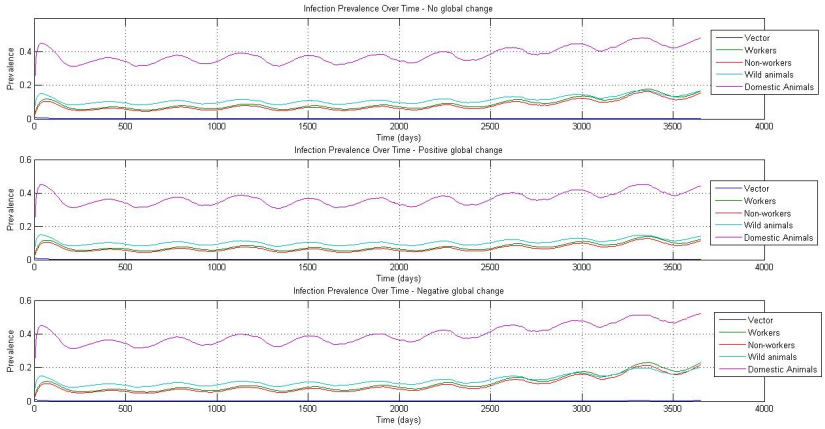

Figure 3. Infection prevalence rates for 10 years. The upper graph represents prevalence rates if no climate change takes place, the middle graph assumes a rise in temperature of 0.015 degrees Celsius per year, and the bottom graph predicts a fall in temperature of 0.015 degrees Celsius per year.

The figure above suggests that if the increase in the mean temperature continues at the same rate over the next decade, the prevalence rates will respond favorably, decreasing at an average rate of approximately 0.2-0.4 percentage points per year. If instead the temperature starts falling at the same rate, the effect will be the opposite. These findings are consistent with our intuition, since the vectors tend to live longer during cooler periods, while the population of hosts remains fixed with time. It is worth pointing

out that the effect of approximately 0.2-0.4 percentage points per year might not seem as a big change relative to the overall prevalence rates, the compounding effect over a longer period (few decades) can lead to much more severe implications as demonstrated on a 10-year chart.

Other potential climate changes include increased daily or seasonal volatility and the convergence of daily maxima and minima towards the mean[30]. While we do not explore such possibilities, our model can easily be adapted to simulate such possibilities.

3.2. *Trapping*

Trapping is the first of the four control strategies we will analyze in this section of the paper. Trapping is an example of a vector control strategy, where the disease is controlled through the eradication of the tsetse flies. We have reason to believe that vector control strategies are in fact highly effective and the existing field studies and theoretical research suggest that there exists a linear relationship between tsetse density and the likelihood of Trypanosomiasis transmission[20].

Trapping is one of the cheapest, oldest, and most well spread control tactics used to both, manage and eradicate the populations of tsetse. The idea of traps is based on the fact that tsetse flies only feed on vertebrate hosts and have hence evolved to detect the possible victims through the use of their senses. An effective trap, hence, mimics the key features of host animals through odor, color, and shape in order to attract the hungry flies[20]. Basic traps function purely through the use of visual stimuli, but their effectiveness can be significantly boosted through the use of odors. The traps kill the flies by either entrapping them or through the use of insecticides.

There are several downsides to trapping, when compared to some other control strategies. Depending on their quality, the tsetse traps are quite prone to physical degradation and can sometimes even be subject to animal and wind damage and even theft. Although minimal, deployment and maintenance of traps does require skilled and available personnel [20]. The effectiveness of traps is a function of the density of traps, density of the vector, likelihood of encounter and the longitude of the traps.

3.2.1. *Trapping Assumptions, Parameters, and Equations*

We assume that the optimal density of trapping for our species is four traps per square kilometer. We base our assumption of optimal density

on the research provided by Hargrove[16] and Dransfield[31] who discovered that an increased density of traps within the range of attraction has stark diminishing marginal returns. An optimal trap density is such that the maximum distance between any two traps is smaller than the expected daily displacement of the fly. With evenly distributed traps at the density of four traps per square kilometer and with the range of attractiveness of one tenth of a kilometer[20], the maximum distance between two traps is 0.253km. Since our species, *Glossina tachinoides*, is expected to travel distances much longer than that, the assumption of four traps per square kilometer is more than sufficient. Hence, within each expected daily displacement our species of fly is almost guaranteed to encounter a trap.

Our general model allows us to uniquely incorporate each control strategy at a fundamental level. Given that the traps are mimicking a vertebrate host, we adopt an assumption that traps are part of the host dynamic with a certain proportion of vectors biting on the traps every day. Of course this proportion is smaller than the proportion of bites taken on actual vertebrate hosts. In our model our default assumption is that the flies will bite on traps 10% of the time. This assumption can be easily modified if better and more expensive traps are introduced. We furthermore assume that every fly that feeds on the trap is guaranteed to die, an assumption that is consistent with the literature[20].

We furthermore assume that the biting preferences are homogeneously distributed throughout the region, with the flies equally likely to bite on the plantation and on the village. This assumption seems reasonable since the two main congregation points for flies are indeed villages and plantations[8]

We also allow for the various proportions of area to be covered in traps under the same assumptions as described above. Hence, our model allows for the possibility that only a certain part of the region (e.g. 40% of the total area) contains traps. Our default assumption is that the trapping occurs throughout the entire region, although some recent literature suggests that such a deployment is unlikely to be maintained efficiently[20].

As mentioned before, the traps require constant maintenance since they are prone to physical damage. Consequently, our model allows controlling for the number of days that the traps are being maintained for with the default assumption being consistent with the literature and set at 365 days.

As observed in the previous section vector population fluctuates significantly with temperature; consequently the timing of trap deployment is important. In light of this fact, our model allows controlling for the start date in order to optimize the effect of trapping.

To incorporate trapping into the general model introduced above, we must modify equations (3) and (4) that measure the rate of change in adult female population and adult male population, respectively. Please note that the teneral population does not need to be modified since they leave the teneral stage immediately after their first meal. Hence, we re-write equations (3) and (4) as:

$$F' = \frac{1}{2}R(C_1 + C_2T)^{-1}(1 - p_t) - F(S_1 + S_2T)^{-1} - (C_1 + C_2T)^{-1}Fp_t \quad (22)$$

$$M' = \frac{1}{2}R(C_1+C_2T)^{-1}(1-p_t)-M(N_1+N_2T)^{-1}-(C_1+C_2T)^{-1}Mp_t \quad (23)$$

where p_t represents the probability of a fly biting a trap, set by default to one-tenth.

3.2.2. *Numerical Results: Default Plot*

We now present and discuss the numerical result for the fully developed model with incorporated trapping. The model was developed and constructed in MATLAB using the equations (1)-(2), (22)-(23), (5)-(9), and equation (20) along with the corresponding values presented in Table 1-3. In the plot presented below, the full model was run for a period of 1000 days and trapping was applied after 1 year in order to minimize the effect of the initial conditions and was in effect for 365 days. As previously discussed, trapping was applied throughout the entire region and the probability of biting on a trap was set at one tenth.

Our initial plot (Figure 4) indicates that the trapping, under our default set of assumptions, is an effective strategy that can lead to effective tsetse eradication. By effective tsetse eradication we refer to an elimination of 99% of the total non-controlled population, since in the majority of cases, theoretical and practical, it is quite impossible to eradicate the population completely[20]. Effective eradication of the vector population in the model above is achieved approximately 343 days after a continuous application of trapping, which supports the established practice of maintaining traps for about a year after deployment in order to achieve operative results. It is also worth noting that there exists a significant lag between the eradication of the tsetse population and the achieved effective eradication of the prevalence rates. The prevalence rates tend to respond slowly to the vector control techniques due to relatively slow disease clearance cycles. In our default plot, the effective prevalence eradication has been achieved

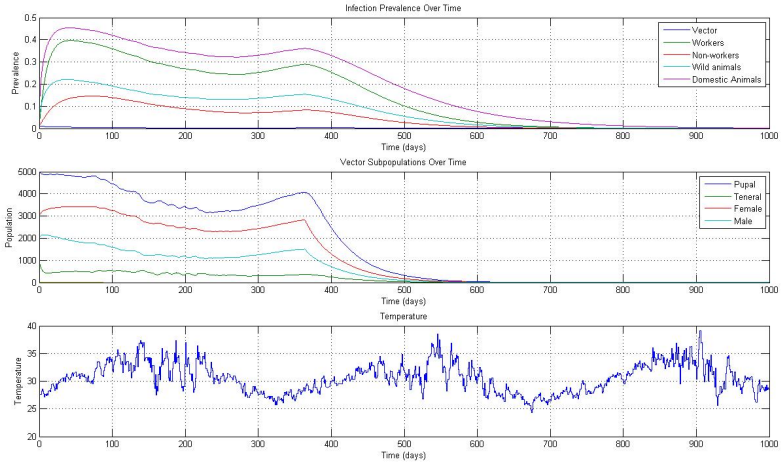

Figure 4. The numerical result for the full model with incorporated trapping that was run for 1000 days. The top graph shows the prevalence rates (percent of the total population infected) for vectors, workers, non-workers, wild animals, domestic animals, and vectors. The middle graph shows the populations for all four different stages of the insect life cycle (pupae, tenerals, female adults, and male adults). The bottom graph shows a temporal stochastic temperature curve with seasonal variance.

approximately 465 after the introduction of trapping to the system, which corresponds to a lag of about 3 months. The existence of such lags is a powerful argument in support of setting up and maintaining the barriers that would prevent re-invasion of flies, even long after the vector population has been eradicated, since a large pool of infected hosts is potentially sufficiently big for the reintroduction of the disease to the system. It should also be pointed out that while the plot above looks very promising, the default assumptions made were quite optimistic. It is often unrealistic to expect that the trapping project can be effectively maintained throughout the prescribed period and region[20] and consequently trapping often doesnt yield the expected results. Nevertheless, the scenario above suggests that if the directions are followed thoroughly, eradication can be achieved.

3.2.3. *Further Numerical Experiments*

Figure 4 provides us with some basic understanding of how the process of trapping control works. However, we're interested in extending our numer-

ical analysis to answer some more nuanced questions. In particular, we will address two of the most important questions related to the optimization of trapping:

1.) Under normal conditions, what time in the year should we start trapping to achieve the most time-efficient eradication?

2.) Under normal conditions, what is the minimum amount of area that we need to trap on in order to achieve effective eradication (95%) of the vector population?

Time efficient trapping

The question of time-efficient trapping is very important, as the main priority of African governments is to eradicate the disease in the fastest time possible[20]. In the research done up until this point, we have showed that the vector population fluctuates significantly with temperature. Hence, we have a valid reason to believe that the amount of time needed to eradicate the disease depends on the starting time. In this section we explore the relationship between the time needed to effectively eradicate the vector population and the time of the year at which we began trapping. In doing so, we hope to contribute to the current discussion of the optimal use of control strategies.

In order to allow for a more realistic comparison across different control methods, we loosen our definition of effective eradication from previously assumed 99% of the initial population eliminated to 95%. For the purposes of this numerical analysis, we construct a model in Matlab, in which we assume that the entire region is being trapped on until the successful effective eradication is achieved. The probability of biting on traps is also fixed at 0.1 and is assumed to be homogeneous throughout the region. We present the summary of our findings in the graph below.

The findings summarized above depict an interesting outcome, and there are a few things worth discussing. It is worth pointing out that the impact of temperature on the effectiveness of trapping is relatively small ranging from 148 days to 154 days. This is a consequence of the fact that effective eradication takes a relatively long amount of time and hence dissipates the immediate impact of temperature. With higher-quality traps, the effect of temperature would be heightened.

Nevertheless, despite being small, the impact of temperature on the overall effectiveness is not completely insignificant and if taken into account can reduce the total amount of time needed by up to a few percentage points. We notice from the figure above that the best time to begin trapping is either in February or during the spring (April-June). Alternatively, the

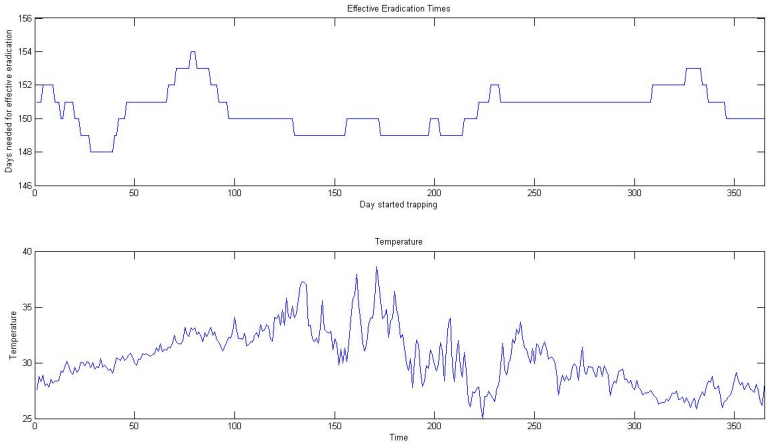

Figure 5. The top graph above presents the number of days needed to effectively eradicate the tsetse population, depending on what day of the year the process is started. The lower graph represents the temperature curve for the given year. The model assumes a set of default assumptions previously discussed.

worst time to start trapping is during March and November.

Area efficient trapping

Deciding what proportion of the region to trap on is often one of the main concerns of capital-constrained non-governmental organizations[20] that are trying to eradicate local tsetse populations in the most capital-efficient way. In answering the previous question, we have given some numerical evidence that temperature plays a small yet not insignificant role in achieving the most time-efficient eradication. In this section, we incorporate these findings and further explore the question of trapping efficiency. In doing so, we hope to provide some meaningful numerical insight into the importance of trapping coverage.

We again assume that effective eradication occurs when 95% of the initial population is eradicated. Incorporating our previous work, we set the day on which we start trapping to be January 29th. Needless to say, the temperature curve for our model will change and it is quite likely that the most time-efficient date will not be January 29th. However, in reality it is impossible to perfectly predict temperature conditions and every decision is hence inherently approximate. We also incorporate an additional assumption that the effective eradication must be achieved in 2 years (730 days).

We find this assumption valid, since the majority of the field data on the topic maintains traps for approximately one to two years.

We construct an additional model in MATLAB in which we again adopt our default set of assumptions and we present the summary of our findings in the graph below.

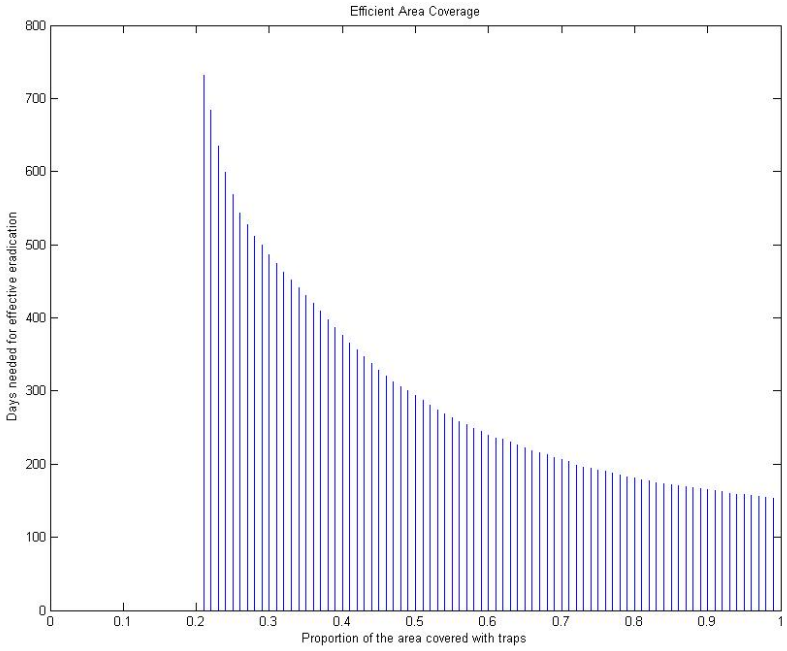

Figure 6. The graph above describes the number of days needed to effectively eradicate the disease, depending on the proportion of the total region covered by traps. A limit of 730 days for effective eradication to take place is assumed.

The figure above suggests that in order to eradicate the tsetse population in less than 2 years, only 22% of the total region needs to be trapped on. It is worth pointing out, however, that this specific limit only refers to this specific region for the default set of assumptions and should in no way be generalized. While to the best of our knowledge there exist no literature that could place this theoretical conclusion into this specific context, the overall results can still be validated on a larger scale. We

notice that if approximately 45% of the region or more is covered in traps, the population will effectively be eradicated in less than a year. Hence, the model supports the general conclusions of the existing field research and control implementation attempts that managed to reach success during comparable time intervals on a comparable scale.

Furthermore, the authors believe that a general relationship between the eradication time efficiency and the area coverage is significant and meaningful. We notice from the shape of the graph that there exist significant diminishing marginal returns to the increase in area coverage. This observation mitigates the concerns that the inaccessible parts of the regions are not being trapped on. Nevertheless, we must bear in mind that our model assumes homogeneous dispersion of the vector, which might not necessarily be true in reality and the impact of area coverage can hence be either reduced or amplified, depending on the situation.

3.3. *Live-Bait Technique*

The live bait technique, including the use of insecticide-treated cattle (ITC), is the second of the four control strategies analyzed. ITC is another example of a vector control strategy and is structurally very similar to trapping, except for the fact that the traps are replaced by live cattle.

The use of insecticides applied to livestock has been developed almost simultaneously with the development of trapping mechanisms and it has seen a tremendous technological improvement over the past 20 years[32].It is widely believed that in areas where there are large numbers of cattle, this is the cheapest and most effective method of vector control[17].

As with trapping, the effectiveness of live bait technique is determined by the quality of spray, pour-on or dip used. While the majority of the commonly-used insecticides are very efficient at killing a fly upon encounter, the products vary widely with respect to the ranges of attraction. Furthermore, an extensive amount of research has been done on the use of footbath treatments vs. full spraying[13] and the two techniques appear to yield very comparable results.

As with any control strategy, there are several downsides to ITC. The control strategy is much harder to manipulate and regulate than the strategy involving only stationary baits. Unlike with the case of stationary baits, it is much harder to manipulate the density of live baits, their location, placement, and movement[17]. Hence, the success of ITC is often determined by factors that cannot be easily controlled and are beyond the

reach of the entity regulating the operation.

The effectiveness of ITC is a function of the proportion of cattle in the region, density of the vector, likelihood of encounter and the duration of regime maintenance.

3.3.1. *Live-Bait Assumptions, Parameters, and Equations*

The live-bait technique can only be applied to cattle and there is very little field research that promises effective results when the technique is applied to other domestic animals. Our general model assumes constant host populations that are based on an estimate of an average sized West African village. Hence, in order to keep the relative size of the village constant, we incorporate the impact of the cattle population on the overall system, by assuming that a relative proportion of the domestic animal reservoir consists of cattle. This assumption allows us to, instead of relying on the absolute values, incorporate the relative cattle proportions into the system, which in turn yield more easily generalizable results. Needless to say, some villages will have higher proportion of cattle with respect to the rest of the domestic animal reservoir than the others. Acknowledging that the value chosen is quite arbitrary and subject to significant change, we decide to assume that 20% of the domestic animal consists of cattle. Thist assumption can, of course, be easily modified within the model.

We assume that cattle are equally likely to be bitten by tsetse flies relative to the rest of the domestic animal reservoir. While this assumption is not true for every case and depends on the insecticide being used, it is hard to generalize about the differences between the biting preferences on different domestic animal species. Although the insecticide applied can often increase the probability of cattle being bitten, the literature also suggests that, absent insecticide treatment, a wide array of tsetse species prefer pigs over cattle[33]. Hence, we decide to keep the biting probability on the entire domestic animal reservoir the same as in the general model, at 0.5. We furthermore assume that the biting preferences are homogeneously distributed throughout the village.

As with trapping, the use of insecticides is time-consuming and requires continuous effort to maintain the effectiveness. Depending on the type of insecticide and the specific technique used (pour-on, dip, spray), the insecticide remains effective for a period of approximately three to seven days[13], after which it needs to be re-applied. We optimistically assume that the insecticide is applied regularly in order to maintain maximum

effectiveness of the control strategy. We furthermore assume that every fly that feeds on the insecticide treated cattle is guaranteed to die, an assumption that is consistent with the literature.

Since the continuous application of insecticide requires time and effort, we decide to incorporate the option to control for the number of days that the cattle is being treated for with the default assumption being consistent with the literature on trapping and set at 365 days (1 year).

As in the previous sections, vector population fluctuates widely with temperature and timing of ITC is important. In light of this fact, our model allows controlling for the start date in order to optimize the effect of ITC.

In order to incorporate trapping into the general model introduced above, we must modify equations (3) and (4) that measure the rate of change in adult female population and adult male population, respectively. Similarly to trapping, please note that the teneral population does not need to be modified since they leave the teneral stage immediately after taking their blood meal. Hence, we rewrite equations (3) and (4) as:

$$F' = \frac{1}{2}R(C_1 + C_2T)^{-1}(1 - \frac{1}{2}dC) - F(S_1 + S_2T)^{-1} - (C_1 + C_2T)^{-1}F(\frac{1}{2}dC) \tag{24}$$

$$M' = \frac{1}{2}R(C_1 + C_2T)^{-1}(1 - \frac{1}{2}dC) - M(N_1 + N_2T)^{-1} - (C_1 + C_2T)^{-1}M(\frac{1}{2}dC) \tag{25}$$

where C stands for the promotion of cattle in the domestic animal population and is initially assumed to be one-fifth.

3.3.2. *Numerical Results: Default Plot*

We now present and discuss the numerical results for the full model incorporating ITC. The model was developed and constructed in MATLAB using equations (1)-(2), (24)-(25), (5)-(9), and equation (20) along with the corresponding values presented in Table 1-3. In the plot presented below, the full model was run for a period of 1000 days and insecticide was applied to cattle after 1 year in order to minimize the effect of the initial conditions and was in effect for 365 days to make results comparable to trapping. As previously discussed, ITC was applied assuming that 20% of the animal reservoir consists of cattle.

Figure 7 indicates that, unlike trapping, ITC, under our default set of assumptions, does not lead to effective tsetse eradication. Please note

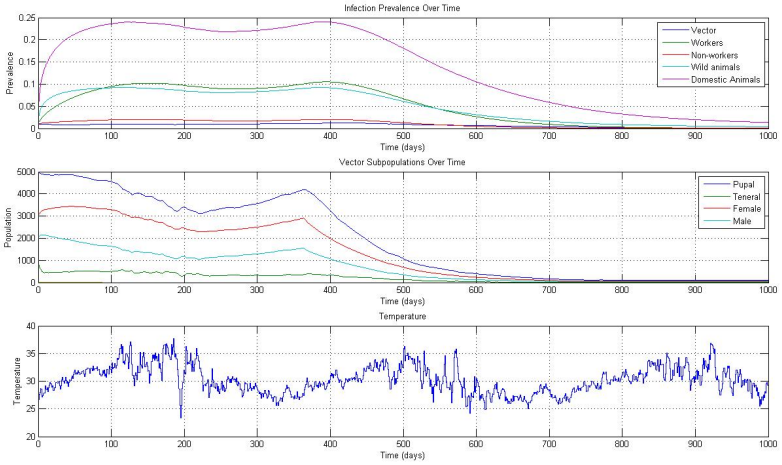

Figure 7. The numerical result for the full model incorporating ITC, run for 1000 days. The top graph shows the prevalence rates (percent of the total population infected) for workers, non-workers, wild animals, domestic animals, and vectors. The middle graph shows the populations for all four different stages of the insect life cycle (pupae, tenerals, female adults, and male adults). The bottom graph shows a temporal stochastic temperature curve with seasonal variance.

that in the analysis of the initial plot we refer to effective eradication as an elimination of 99% of the total non-controlled population. We loosen this assumption to 95% of the population eradicated when analyzing the further numerical experiments in the next section. While effective eradication of the vector population is not achieved, the initial plot does suggest that the strategy clearly works and is quite successful at lowering the vector population. In fact, the insecticide-treated cattle technique eliminated approximately 97% of the population within the first 343 days after it was introduced to the system (note that it took 343 days to successfully eradicate 99% of the vector population when the trapping was applied). Hence, although not as efficient under the default assumptions ITC proves to be quite comparable to trapping, which is widely supported by the literature[17].

Again, it is also worth noting the significant lag between the eradication of the tsetse population and the eradication of the prevalence rates. Since ITC under default assumptions removes the vector population more slowly than trapping, the eradication of the actual disease from the system is consequently slower as well. After 465 days since the introduction of ITC,

the approximate amount of time it took to effectively reduce the prevalence rate through the use of trapping, the prevalence rates still remain quite significant fluctuating at approximately 10% of their initial values before the insecticides were applied to cattle. Non-negligible prevalence rates that persist in the ecosystem long after the application of insecticides to cattle is discontinued are also a direct consequence of the non-negligible vector population that has not been completely eradicated by the control strategy. The issue of careful maintenance and regulation of control regimes is even more important when effective eradication has not been fully achieved.

3.3.3. *Further Numerical Experiments*

As we did with trapping, we can now extend our numerical analysis to expand our understanding of ITC as a control technique and apply our model to some more nuanced questions. Since ITC is structurally quite comparable to trapping, it should be of no surprise that the important numerical questions are similar. We will address two of the most interesting questions related to optimization:

1.) Under normal conditions, at what time in the year should we start continuously applying insecticide to achieve the fastest eradication?

2.) Under normal conditions, what is the minimal amount of cattle that can be owned relative to the size of the fixed domestic animal reservoir in order to still achieve effective eradication (95%) of the vector population?

Time efficient application of insecticide to cattle

As previously noted, the question of optimal timing is vital in achieving both quick and cost-efficient application of the control strategy. Again, we utilize our temperature-dependent model to address the question of optimal timing through a numerical experiment and hopefully contribute some valuable insight on the overall understanding of ITC efficiency and timing. In order to numerically examine this relationship, we construct a model in MATLAB in which we assume that 20% of the domestic animal population is constituted by cattle and that the entirety of the cattle population is treated with the insecticide. Effective eradication is defined as 95% reduction from initial population values. We present the summary of our findings in the graph below.

The findings summarized in Figure 8 above provide some interesting insight on the topic of time efficient eradication using ITC. We notice that the impact of temperature is significant and a proper choice of timing can reduce the total period of insecticide application by up to 25 days, about 8%

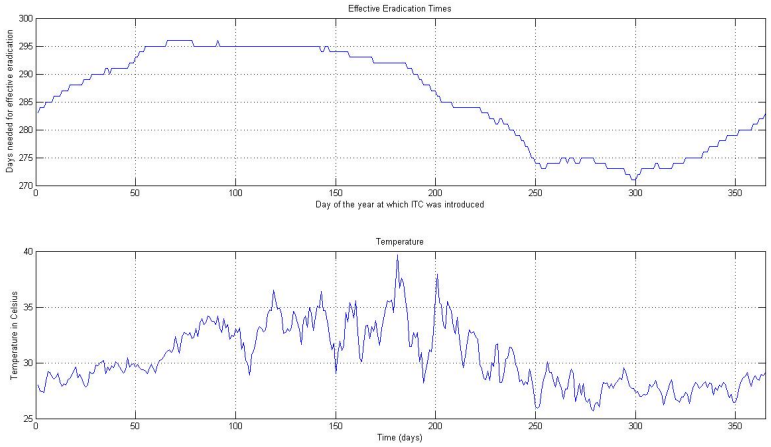

Figure 8. The top graph represents the number of days needed to effectively eradicate the disease, depending on what day of the year the process is started. The lower graph represents the temperature curve for the given year that remained fixed for each scenario. A set of default assumptions previously discussed is assumed.

of total time to eradication. Compared to trapping, the overall relationship between the start date and time needed until eradication is stronger and less scattered, suggesting that the temperature and optimal timing play a more important role. We contribute this outcome largely to the fact that longer eradication period does a better job of smoothing the impact of random temperature spikes.

Based on our numerical analysis, we conclude that the best time to start applying insecticide to the cattle is in early autumn (end of August, September, beginning of October) which will, assuming our wide range of default assumptions, result in the fastest eradication of the vector population. Conversely, if ITC is introduced in a period from February-April, we should, according to our model, expect the longest eradication period. Linking these observations with the corresponding temperature curve, we observe that, in general, if ITC is being applied during the periods of relatively lower temperatures, the corresponding eradication time is significantly shorter than if ITC is instead being introduced during periods of higher temperatures.

Required minimum proportion of cattle

Up until now we have assumed that the proportion of the animal reser-

voir that is cattle was set at 20%. While this is not an unrealistic assumption, the value of this parameter varies widely between locales and needs to be addressed accordingly. It should be obvious that as the proportion of cattle in the village increases, the success of ITC will increase proportionately. In this part of the numerical analysis we will explore the relationship between effective eradication times and the proportion of the cattle in the domestic animal population. In doing so, we hope to provide a meaningful threshold for determining whether an application of ITC is practical or not.

We, again, assume that effective eradication occurs when 95% of the initial population is eradicated. Incorporating our work on time efficient ITC application, we set the day on which we start applying insecticide to cattle to be October 27th. We also incorporate an additional assumption that the effective eradication must be achieved in 2 years (730 days). In order to control for the size of the village, the only parameter that will change is the proportion of cattle (the size of domestic animal reservoir remains fixed at 50 animals). We adopt our default set of assumptions along with the discussed modifications to construct an extended model in MATLAB. We present the summary of findings in the figure below.

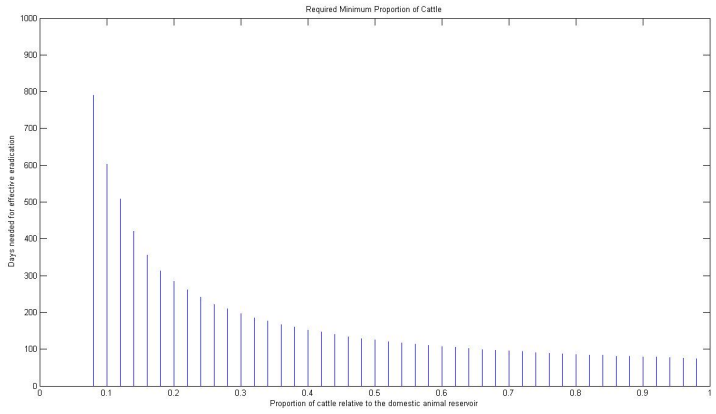

Figure 9. The graph above describes the number of days needed to effectively eradicate the disease, depending on the proportion of cattle in the domestic animal population.

Figure 9 suggests that in order to eradicate the tsetse population in less than 2 years, using ITC, only 10% of the domestic animal reservoir needs to consist of cattle. Furthermore, cattle only need to represent approximately

16% of the reservoir in order to bring down the effective eradication period under a year. It is worth pointing out, however, that this specific limit only refers to this specific region for the default set of assumptions and should not be freely generalized.

It is interesting to observe the shape of the relationship, which indicates that ITC is almost as effective in the villages with 70% cattle as it is in villages with cattle being the only domestic animal. This result is viable and is a consequence of the fact that the domestic animals are only one potential host for tsetse fly, which mitigates the impact of cattle proportion increase. Furthermore, the observed relationship suggests that the proportion of cattle does need not to be large for ITC to be effective. This observation mitigates the concerns that only the villages with very high proportion of cattle should be pursuing ITC.

We also notice that as the proportion of cattle increases, the period needed for effective eradication is effectively reduced below the period needed for eradication under trapping. This observation is consistent with literature and field data that indicate that for certain villages with high proportion of cattle, ITC is a faster and more effective control strategy than trapping[17].

3.4. *The Sterile Insect Technique*

The sterile insect technique (SIT) is the third of the four control strategies that we will analyze and the last example of a vector control strategy considered herein. While not as old or widespread as trapping and ITC, the concept of releasing sterile insects into wild populations has been around since for at least seventy years[34]. An extensive amount of research has been done on the topic and the process of SIT application is well understood.

The underlying principle of SIT is that fertile adult tsetse female flies are incapable, to a certain extent, of producing larvae after they have mated with a sexually sterile male. The process of sterilization of adult males is usually completed through mutagenic agent treatment, such as for example gamma radiation or chemosterilants application[35]. After such treatment, the sterile males are released into the wild to freely mate with the wild adult female flies. The success of the entire process is heavily dependent on the assumption that the sterile males, aside from being infertile, display the same behavior as their wild equivalents[35]. Although the literature reviewed usually adopts such an assumption as valid, there are some authors that account for poor performance of sterile males when compared to wild

counterparts[19].

As with any control strategy, there are several shortcomings to using SIT. When compared to trapping and ICT, SIT is usually a much more expensive and less accessible control method, especially when the area controlled is large[17]. Furthermore, effective eradication is usually easier achieve through the use of more conventional control methods. Although not often[17], SIT can be used to achieve effective eradication of the vector, although it is more often used to merely reduce insect populations to very low levels[35]. Nevertheless, it is also worth mentioning that the use of SIT is rather environmentally friendly and it does not assume any of the risk that the flies treated with insecticides will develop resistance to the chemicals.

The effectiveness of SIT is a function of the number of sterile males released compared to the overall vector population, the overall comparable performance of sterile males relative to their wild counterparts, frequency of mating, and replacement proportion of previously deposited sperm.

3.4.1. *SIT Assumptions, Parameters, and Equations*

We assume that sterile males introduced into the system exhibit poor performance relative to their wild counterparts. We incorporate this assumption to be consistent with the majority of the recent literature on mathematical modelling[19] that strives not to overstate the impact of SIT on the vector population. Hence, consistent with literature, we assume that the sterile males have 25% greater death rate than their wild counterparts[19]. If other control strategies are introduced into the system the sterile and wild males are equally susceptible to their impact.

The females inseminated by sterile males have a high chance of becoming infertile. Nevertheless, the fertilization process is rather complicated and further assumptions need to be addressed. A large portion of entomological research on tsetse fly behavior seems to suggest that female flies only mate once in their lifetime. In fact, in our previous research on the topic, relying on such literature, the authors have made a similar assumption[25]. While this assumption was rather irrelevant up until now and has not impacted the overall behavior results, we must now take special care to revise it appropriately. Based on the entomological research provided by Dame and Ford[23] we are able to conclude that an assumption of multiple mating is valid. It is worth noting that had we not changed our assumption from previous research, our results of SIT effectiveness would be decidedly skewed. Although the research provided by Dame was performed on

a different species of tsetse fly than assumed in our model, we base our parameter estimates on their results, due to the lack of better data. We do, however, acknowledge that such parameter estimates are very approximate and need to be subject to further revisions as more research is done on the topic. Basing our estimates on the lab experiments presented by Dame and Ford, we conclude that a female that has mated with a sterile male first and fertile male second will deposit the pupa 44.7% of the time. Conversely, a female fly that has first mated with a fertile male and with a sterile male second deposits a pupa, on average, 85% of the time[23]. No change in pupa deposition rate is assumed if the fertility of consecutive male mating partners does not change and the flies are assumed to mate, on average, every three days.

Mating probability is a direct function of the size of sterile male and wild male populations, an assumption consistent with what is suggested in the literature[23]. Hence, a simplifying assumption is made that if a female was last inseminated by a sterile male it will assume the pupa production capacity of a previously assumed infertile female. If conversely, a female was last inseminated by a wild male, it will assume the fertile rate of production of pupa. It needs to be stated that such an assumption ignores some of the nuances related to mating process and sperm replacement rates for tsetse flies as there exist proven diminishing returns[23]. However, as pointed out previously, since such data is not available for our specific species, we avoid making unnecessary ungrounded assumptions and instead assume linearity.

Acknowledging the complexity of the discussed technique we build our model in such a way to allow the researchers to freely determine the number of releases, the number of males released, the possible increase in releases, and the starting time of SIT. We do not, however, allow for variance in the intervals between the consecutive releases since our research indicates suggest that this is difficult to control. Hence we assume that the males are released weekly, basing our parameter estimate on the model introduced by Vale and Torr[19].

While we allow for a free modification of the parameters described above, we also provide the initial parameter estimates (default values) based on the existing research done on the topic to stimulate the discussion. Hence, we set the number of males(m_i) released each interval at three times the population of wild males (about six thousand), a ratio that Vale and Torr found to be an optimal estimate[19]. We furthermore set the rate of increase (m_r) in size of successive releases to be zero, consistent with Vale and Torr. The number of weekly releases (R_W) is initially set at six.

Our vector population submodel allows us to uniquely incorporate the impact of sterile male releases into the system by more precisely modelling their overall behavior. In order to incorporate SIT into the system, we hence create two additional tsetse subpopulations, sterile males and infertile females. As discussed in the previous paragraphs, aside from their infertility (females), their sterility (males), and their weaker immune system causing higher death rate (males), the underlying assumptions for these two stages remain the same as for the rest of the population. We model the sterile males (M_S) with the following equation:

$$M_S' = m_i(1 + m_r)^{R_W} - 1.25(N_1 + N_2T)^{-1}M_S \tag{26}$$

Where m_i denotes the number of males released at each interval, m_r denotes the increase rate, and R_W represents the number of releases. Similarly, the infertile female (F_S) rate of change is as follows:

$$F_S' = \frac{M_S}{M_S + M}\frac{1}{3}(f_f F - f_i F_S) - (S_1 + S_2T)^{-1}F_S \tag{27}$$

Where $f_f = 0.85$ and $f_i = 0.447$ denote the ability of fertile and infertile female flies to produce pupae, respectively. In order to account for the impact of sterile males on wild females, we must also modify equation (3) which models wild female population by adding a loss term to the sterile females compartment.

$$F' = \frac{1}{2}R(C_1 + C_2T)^{-1} - F(S_1 + S_2T)^{-1} - \frac{M_S}{M_S + M}\frac{1}{3}f_f F \tag{28}$$

3.4.2. *Numerical Result: Default Plot*

We now present and discuss the numerical results for the fully developed model with incorporated SIT. The model was developed and constructed in MATLAB using the equations (1)-(3), (26)-(28), (5)-(9), and equation (20) along with the corresponding values presented in Table 1-3. In the plot presented below, the full model was run for a period of 1000 days and sterile males were began to be released after one year in order to minimize the effect of the initial conditions. As previously discussed, 6000 sterile males (3:1 ratio) were released every seven days for six consecutive weeks.

Figure 10 suggests that, under the set of our default assumptions, SIT is unable to achieve effective eradication at both, 99% and 95% level, as

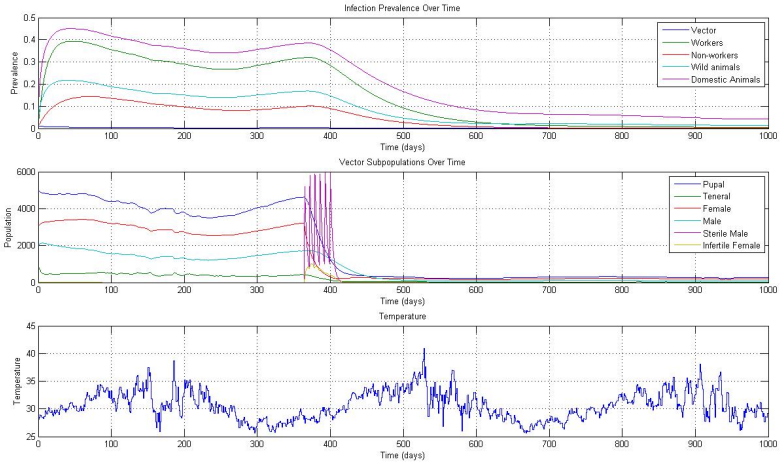

Figure 10. The numerical results for the full model with incorporated SIT, run for 1000 days. The top graph shows the prevalence rates (percent of the total population infected) for vectors, workers, non-workers, wild animals, and domestic animals. The middle graph shows the populations for six different stages of the insect life cycle (pupae, tenerals, female adults, male adults, infertile females, and sterile males). The bottom graph shows a temporal stochastic temperature curve with seasonal variance.

a significant portion of the vector population remains alive after the sixth consecutive release of sterile males. This observation is consistent with the existing literature, which suggests that SIT, if the only control strategy applied, will often not achieve effective eradication[19]. It is also worth pointing out that we do not assume any emigration of the sterile males released into the wild. Hence, our numerical analysis, unless controlled for migration, might, to an extent, overestimate the effectiveness of SIT.

Nevertheless, despite the fact that SIT application does not achieve effective eradication, it should be observed that it is by far the fastest acting control strategy, when compared to trapping and ITC. Hence, our numerical analysis indicates that although SIT is expensive and less efficient in achieving effective eradication, it is a control strategy that should be seriously considered when immediate vector population reduction is required.

However, despite reducing the vector population at a rapid rate, SIT fails to achieve the same when it comes to a reduction of prevalence rates that remain sluggish and relatively high. The failure of SIT to achieve the same results in our prevalence submodels as the other control strategies is a

consequence of the lags previously discussed coupled with reduced, yet still significant, vector populations which remain alive after SIT is discontinued.

3.4.3. *Further Numerical Experiments*

Because of its structure that allows free variations in a wide array of parameter inputs, the optimization question for SIT becomes much more complex than it was for trapping and ITC. We will address two of the most interesting questions related to optimization:

1) Assuming slightly modified default conditions, at what time in the year should we start releasing sterile males in order to achieve the most time-efficient eradication?

2) How does an increase in number of releases and in total males released impact the effective eradication period? In other words, what combination of number of releases and number of males released results in the least amount of total sterile males used while still achieving effective eradication?

Time efficient implementation of SIT

Similarly to the numerical analysis of trapping and ITC, we first focus on utilizing our temperature-dependent model to analyze the time efficient implementation of SIT in order to provide some initial insight into a complex relationship between starting times, temperature, and time efficient control strategy applications.

We concluded in the previous subsection that our default set of assumptions will not lead to effective eradication at 95% level. Hence, we now slightly modify and revise our parameter values in order to enable an expedient analysis of time efficiency. To minimize the impact of revisions, we decide to only modify the number of total releases, increasing them from six to eight. We believe that this is a reasonable revision that does not significantly change the overall behavior of the system, while simultaneously leading to desired effective eradication level of 95%.The rest of the assumptions remain unchanged with the number of males released set at 3:1 ratio when compared to its wild population, the interval between the releases set at seven days, and the rate of increase set flat at zero. We present the summary of our findings in the graph below.

The findings summarized in Figure 11 indicate that if SIT is applied during the periods of higher daily temperatures, the time to achieve effective eradication will be significantly faster than if instead SIT is implemented during the periods of lower temperatures. This relationship between the effective eradication times and temperature suggest that there is a strong

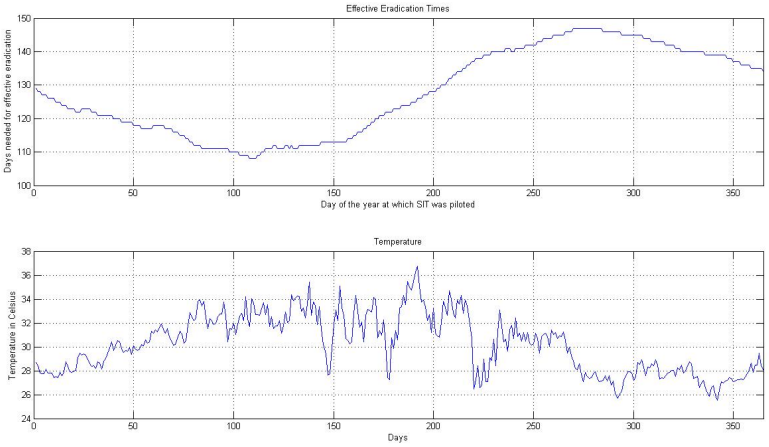

Figure 11. The top graph represents the number of days needed to effectively eradicate the disease, depending on what day of the year SIT process is initiated. The lower graph represents the temperature curve for the given year that remained fixed for each scenario. A set of slightly revised default assumptions, discussed previously, is assumed.

correlation between the number of flies in the system and the effective eradication period. Such a relationship is also observed in the literature and the model supports the notion that SIT is most effective in the final stages of the disease eradication process, when the vector population is already significantly reduced. This makes SIT a pronounced complement to trapping and ITC, since as we observed in their analysis, there exist significant diminishing returns to their effective eradication times.

We also notice that the impact of temperature on the overall length of effective eradication is much more prominent and significant for SIT than it was in case of trapping and ITC. Our model suggests that with optimal timing we can decrease the length of the eradication period by up to 40 days, which accounts for approximately 27% reduction from the worst case scenario assumed by the model. The main reason why the impact of temperature is that much more noticeable in case of SIT implementation is due to the fact that SIT tends to achieve effective eradication much faster than trapping and ITC. Hence, the immediate state of the vector population and prevalence rates are that much more important as the temperature effect does not get mitigated through a long time period.

Resource efficient implementation of SIT

In our analysis of SIT up until now, we have held fixed the majority of the parameters that can be varied such as number of releases and males released. In this part of the analysis, however, we explore the role of these parameters with respect to time efficiency and optimal resource allocation. In performing such numerical analysis, we strive to provide some important insight into how should the control strategy be implemented in order to optimize the amount of resources used and time spent.

We, again, assume that effective eradication occurs when 95% of the initial population is eradicated. Incorporating our work on time efficient SIT application, we set the day on which we start implementing SIT to be April 20th. We furthermore assume, as previously discussed, that the rate of increase remains flat and that the males are released every 7 days. We then vary the number of releases and the number of males released and explore the impact of these incremental changes on the corresponding effective eradication rates. This analysis allows us to determine the most resource-efficient and time-efficient combination of varied parameter values. We present the summary of findings in the figure below.

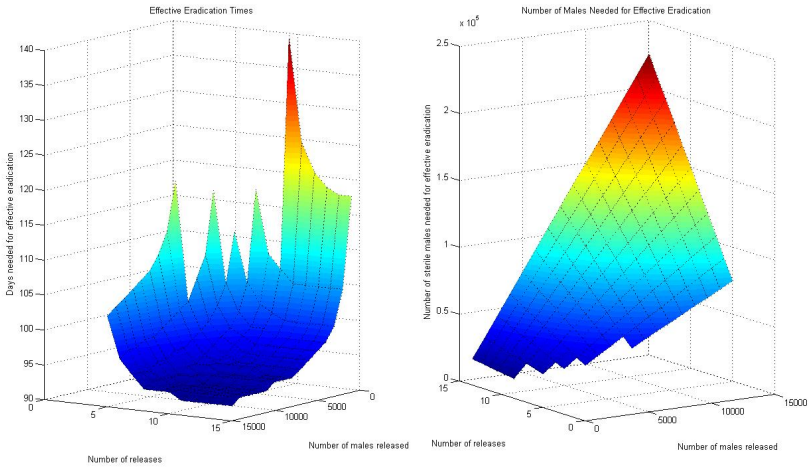

Figure 12. The graph on the left represents how the effective eradication times vary with respect to the number of releases and number of males released with each release. The graph on the right complements it as it represents the total number of sterile males that needed to be used for each of such scenarios.

The two graphs in figure 12 above offer an interesting perspective. Our

numerical analysis suggests that the number of releases plays a much more prominent role in determining the resource efficiency than the number of males released during each interval. As few as 10,000 sterile males total are needed to eradicate the disease if they are released at the rate of 1,000 males per interval. Quite reasonably, however, the most resource efficient approach is also the slowest, as it achieves effective eradication 48 days later (approximately 52% longer) than the fastest and most resource intensive approach.

Conversely, the graph on the left indicates that the time-efficient eradication strategy is much more sensitive to the increase in the number of sterile males released at each interval. We link this fact to the point made in the previous subsection, where our analysis showed that the overall ratio of sterile to wild males plays a crucial role in determining the overall eradication period. Hence, our analysis further supports the argument that the absolute and relative time efficiency of SIT increases proportionally with the size of the regions.

3.5. *Screening*

Screening is the fourth and the last control strategy introduced, described, and analyzed in this work. Unlike the first three control strategies analyzed, screening is not an example of a vector control strategy. Screening instead targets the human reservoir directly and is generally introduced to reduce mortality by identifying cases early and to reduce future transmission rates by eliminating a portion of the infectious host reservoir [18].

T.b. gambiense HAT, the chronic version of HAT, has two stages: the first or hemolymphatic stage and the second or neurological stage of the disease. In the first stage of the disease, patients experience nonspecific symptoms such as fever, headaches, arthralgia, and enlarged cervical lymph nodes. In the second stage, psychiatric, sensory, and motor functions are interrupted, and if left untreated, the patients die due to eventual dysfunction of the immune system [15]. The process of screening is non-trivial and the disease is diagnosed in three steps: screening, diagnostic confirmation, and staging (first or second stage)[15]. The majority of active screening methods are based on mass case detection and must hence be affordable, quick, sensitive, and sufficient in its capacity[15].

There exist several methods for active screening. Currently, the most well used method is Card Agglutination Test for Trypanosomiasis (CATT) that allows hundreds of individuals to be tested daily. CATT is a simple

agglutination for detection of antibodies in the blood, plasma, or serum of HAT patients and its reported sensitivity varies from 87%-98%[15]. Nevertheless, due to its sensitivity CATT remains limited as it is difficult to apply to regions with HAT prevalence rates lower than 5%.

Once an infected individual is successfully detected through the use of CATT or any other method, he must go through staging in order to determine a suitable treatment. If individual is in the first stage of the disease, a 7-10 day treatment with intramuscular pentamidine is prescribed and less than 1% chance of dying is assumed. Patients in the second stage are instead treated with melarsorpol and 2%-10% mortality rate is assumed[15]

The effectiveness of screening is a function of five factors: attendance rate, sensitivity of the screening test, sensitivity of the confirmation test, proportion of confirmed cases that complete treatment, and cure rate[18].

3.5.1. *Screening Assumptions, Parameters, and Equations*

In order to incorporate the impact of active screening on the overall prevalence in humans, we adopt a model developed by Robays et al[18] in which the otherwise complicated process of active screening is simplified and broken down into five components that in turn determine the effectiveness of the method. As previously mentioned, the effectiveness of screening (E) is defined as a product of attendance rate (A_r), sensitivity of the screening test (S_s), sensitivity of the confirmation test (S_c), treatment completion rate (T_r), and cure rate (C_r).

In their paper, Robays et al also provide a range of estimates for each parameter. For the purposes of the thesis, we decide to assume the mean values. In this paper we provide the readers with the chosen mean estimates, but we omit the justification and the range values as they are easily accessible in the original paper[18]. Hence, we obtain the following equation for the effectiveness of active screening:

$$E = A_r S_s S_c T_r C_r \tag{29}$$

The initial values are: $A_r = 0.75$, $S_s = 0.95$, $S_c = 0.75$, $T_r = 0.9$, $C_r = 0.9$, and $E = 0.43$.

The overall success of active screening also depends on the optimal frequency of the screening rounds, which is still poorly understood and widely debated[18]. Some prominent researchers recommend three separate screening rounds at one-year intervals, while others use 6-month intervals.

According to Robays et. al, the most recent research assumes 6-month frequency, which will be also a default parameter value for our model. We assume that four screens are conducted, composing a two year long program.

Since active screening is quite expensive and hard to implement within large communities, we also incorporate an option to control for the proportion of the population screened and for the population subtypes (workers and non-workers). Since active screening programs usually strive to screen the entire population, we assume in our default set of assumptions that the entirety of both worker and non-worker populations are screened each time.

Although to a lesser extent our initial plot of the general model shows fluctuations in prevalence rates due to temperature impact. Hence, in order to address the question of optimal timing, we also allow to vary the starting times at which the first screen is piloted.

In order to implement the discussed additional assumptions into our model, we only need to modify the equations for the prevalence rate schange in workers and nonworkers. Hence the modified equation for workers is given as follows:

$$W' = (6) - sW_S EW \tag{30}$$

Here W_S is the proportion of workers screened, E is the effectiveness of screening, and s is the inverse frequency of the program. Similarly, if we use N_S to represent the proportion of non-workers screened, the modified equation for non-workers is given as:

$$N' = (7) - sN_S EN \tag{31}$$

3.5.2. *Numerical Result: Default Plot*

We now present and discuss the numerical result for the fully developed model with incorporated active human screening program. The model was developed and constructed in MATLAB using the equations (1)-(5), (30)-(31), (8)-(9), and equation (20) along with the corresponding values presented in Table 1-3. In the plot presented below, the full model was run for a period of 1000 days and active screening was first piloted after one year in order to minimize the effect of the initial conditions. As discussed previously, the program screened the entire population four times in intervals of six months.

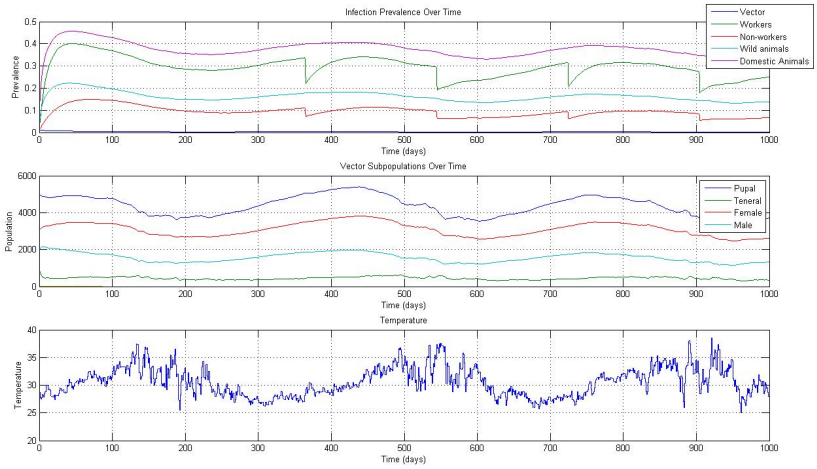

Figure 13. The numerical result for the full model with incorporated active screening program, run for 1000 days. The top graph shows the prevalence rates (percent of the total population infected) for workers, non-workers, wild animals, domestic animals, and vectors. The middle graph shows the populations for four different stages of the insect life cycle (pupae, tenerals, female adults, male adults). The bottom graph shows a temporal stochastic temperature curve with seasonal variance.

The results presented in the plot above are consistent with our previous discussion and help explain why overall success of active screening is widely debated[18]. Screening provides an immediate relief to 43% of the infected human population and is much faster in achieving its goal than the vector control strategies discussed on previous pages. Nevertheless, screening when applied solely, fails to achieve any long term eradication as the prevalence rates in animal reservoir and unaltered vector population are sufficient to bring the human prevalence rate back to its long run equilibrium even before the next screening is piloted in the region. Hence, our results suggest that screening should always be coupled with a vector control strategy that effectively reduces the prevalence rates and vector populations and amplifies the impact of the program.

It should also be noticed that the results above suggest that the amount of time it takes for the human prevalence rates to return back to its pre-equilibrium state depends on when the screening is applied in the region. For example, it takes the workers' prevalence rate 79 days to achieve its pre-screen value after the first screen and 174 days to do the same after

the second screen is applied. This observation is consistent with what we observed in the general model and serves as the underlying motivation for our additional numerical experiment.

3.5.3. *Further Numerical Experiments*

Since screening in a multi-host system is not sufficient to effectively eradicate the disease, the analysis of optimal effective eradication is not applicable. Nevertheless, motivated by the observation in the previous section, we decide to instead analyze the efficiency of an impact that a single screen has on the total number of human infections prevented. As mentioned previously, some researchers on the topic recommend that screening is performed annually[18] and repeated three times. Hence, given the fact that the prevalence rate behavior varies with time, we set to numerically explore at what time the screening should be administered to maximize the number of infections prevented. We hope that our numerical experiment will provide some meaningful insight into the optimization of timing of active screenings.

Optimal Screening Times

In order to answer the question of optimal screening times, we construct a model in MATLAB that, for each day in a year and for a fixed temperature curve, compares the number of infection days prevented by a single implementation of screening. In order to amplify the differences and obtain a clearer picture, we assume that the effectiveness of screening is perfect (i.e.$E = 1$). An example of how the human prevalence rate (workers and non-workers) changes when screening is introduced is given in the following figure:

As Figure 14 indicates, screening is only a temporary solution and the human prevalence rates for the two different scenarios assumed soon converge. Hence, we can explore during what times the introduction of screening maximizes the area between the two curves. We present our final results in the figure below.

Figure 15 provides convincing evidence for importance of optimal timing on the overall success of active screening. If the screening is implemented at a time of the year during which the temperature is expected to rise or to remain high, the impact of screening will be much more significant than if the method is implemented during the cooler periods of the year. It is also worth noting, however, that there does exist a lag between the impact of such cooler/warmer periods and the correspondent reaction. This lag

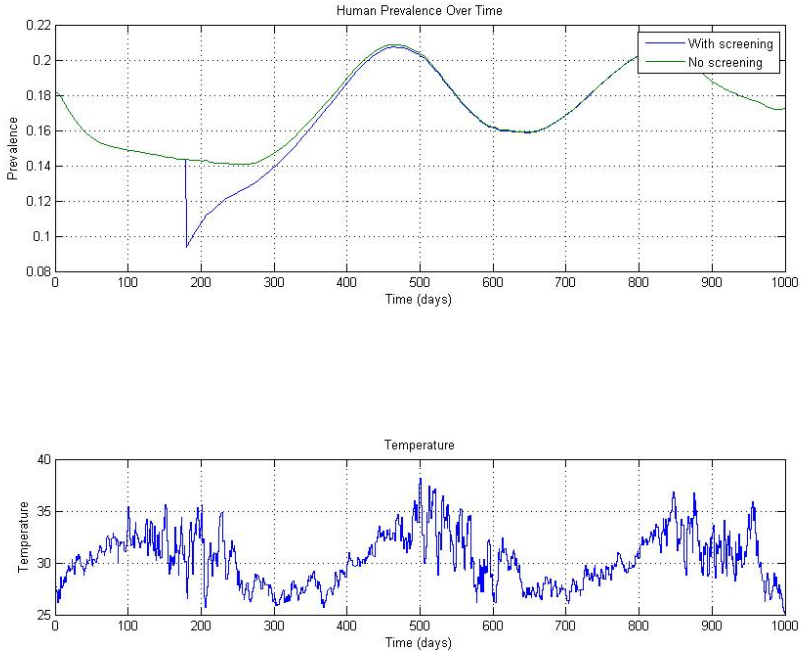

Figure 14. The figure above depicts an example in which the screening is introduced on June 29th (180th day in a year) and compares its effect on human prevalence with the scenario in which no control strategies are introduced.

is consistent with the qualitative pattern described in our previous section and is a consequence of a lag between the prevalence submodels and the insect population submodel.

Similarly to SIT, the process of screening is sensitive to the fluctuations in temperature. Our analysis suggests that with optimal timing, the number of total infection days prevented can be increased by up to approximately 25% with respect to the worst timing for control implementation. The increased sensitivity of the control strategy is, just like in SIT, a function of its rapid impact on the system behavior, which amplifies the importance of temperature. Hence, we conclude that, due to temperature-dependency, a careful consideration of when to screen is of vital importance for the overall success of the program.

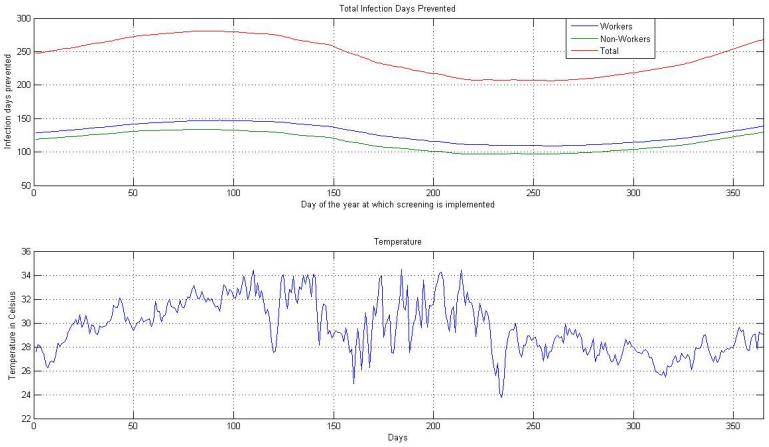

Figure 15. The top graph above represents the number of total infection days prevented as a result of a screening for workers, non-workers, and the entire human population. The lower graph represents the corresponding temperature curve that was held fixed throughout the numerical investigation.

3.6. *Barriers and Invasion*

As explained at the beginning of the section, we based our analysis of the control strategies on the underlying assumption that the region is either naturally isolated or that an effective barrier set-up is used. Such an assumption allowed us to focus solely on the impact of the control strategies on the system without any external factors altering its overall behavior. In this last part of our numerical work we drop this assumption and briefly analyze the importance of setting up such barriers in the regions prone to fly invasion.

In his research on the invasion of cleared areas by tsetse flies[36], Hargrove points out that there seems to be little thought given to the fact that the majority of the new policies tend to contain instead of eradicate the tsetse population. The areas where tsetse are not been completely eliminated create the possibility of re-invasion, and indeed, the old equilibrium can be introduced within a matter of a year since clearance[36].

Since it is becoming more and more prevalent that the control strategies target specific areas, where there is farming or some sort of other income-generating activity[36], we must pay special attention to the possibility of vector re-invasion from uncontrolled surrounding areas. Our model lends

itself as such example as it is designed specifically for a village-plantation module and does not concern itself with alternative control measures, such as control of large area blocks. Due to insufficient funding this module is an appropriate and prevalent approach to the control of the disease[36]. However, its success is only guaranteed if an appropriate barrier system is set up and maintained fittingly.

In order to demonstrate the devastating impact of invasion and emphasize the importance of barrier set-up, we extend our model to assume external recruitment rate. The modifications are based on the idea that as we start to control the local tsetse population, we deviate from the implied local carrying capacity and the flies from the outer regions begin to migrate into the controlled area until the implied carrying capacity equilibrium is re-established. For simplicity, we assume that the vectors are migrating at a constant rate and from the entirety of the surrounding area. We make an assumption that a totally cleared area of our size (less than a hundred square kilometers) has a complete replacement rate of 180 days[36]. In order to incorporate the impact of a barrier set-up, we assume that an eight-kilometer-wide barrier is set with a density of four traps per square kilometer, and effective probability of penetration of 0.001[20]. Needless to say, such barrier set-up is very extensive and often barriers will be much smaller. Nevertheless, for the purposes of demonstration, an optimal approach to barrier set-up that almost entirely mitigates the impact of re-invasion and practically assumes isolation is adopted.

For the sake of brevity, we only demonstrate the impact of re-invasion and the barrier set-up solution for an example of trapping application. Trapping is applied after 365 days and is in effect for a period of 365 days. The results are summarized in Figure 16.

Figure 16 provides a clear reason as for why the majority of contemporary researchers emphasize the importance of setting up an effective barrier system. If external migration is incorporated and no barriers are set up, the effective eradication achieved through trapping is mitigated completely. Furthermore, the process of trapping itself is significantly less efficient as the flies started migrating into the region as soon as the control strategy is introduced. If, however, a control strategy is implemented when the barriers are set up, the impact of external migration is due to our assumptions, expectedly, almost completely mitigated.

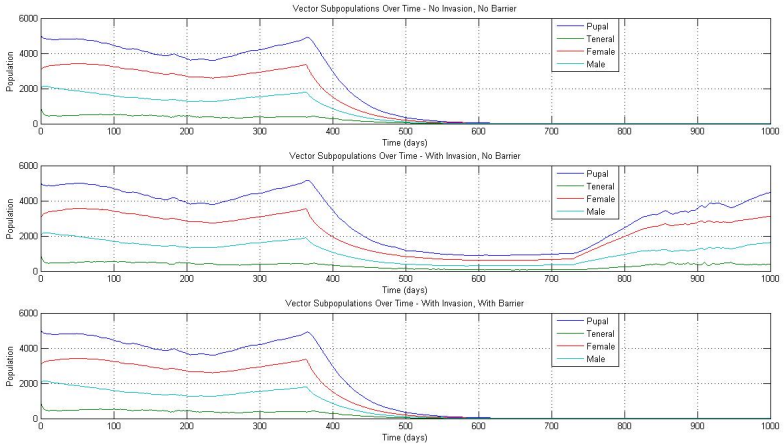

Figure 16. The top graph demonstrates the impact of trapping in an isolated area. In the middle graph, external migration is allowed and no barriers are incorporated. In the bottom graph, external migration is allowed and the barrier set-up is fully incorporated.

4. Discussion

Human African Trypanosomiasis is a neglected disease and its overall impact on the worlds poorest regions is severely understated. The existing field research on the disease is thin and the funding available is insufficient. As a result, the disease is poorly investigated and there exists a dire need for the involvement of applied mathematicians who can provide significant and meaningful initial insight into the disease behavior without necessarily relying on the extensive funding required to conduct large scale field research. In this thesis, the authors decided to build on the extensive amount of work done on the topic over the past two years with intent to directly address what is the most important question of this type of disease research, namely methods of disease control and eradication. Hence, the purpose of the thesis is twofold. Firstly, we strive to develop a comprehensive temperature-dependent non-autonomous ODE model that is generally applicable to a variety of situations and will allow us to analyze and further understand the disease behavior despite the lack of epidemiological data. Secondly, we utilize the developed model to provide meaningful numerical analysis and insight into suitable and optimal application of various control strategies. In doing so, we hope to provide valuable insight where the exist-

ing research falls short and to contribute to the noble mission of effectively controlling the disease.

We construct a model that couples the temperature-dependent, rapidly-migrating vector population with the epidemiology submodels for the animal and human hosts. The model is based on a wide array of findings provided by the established literature and derived by the authors over the past two years such as the importance of patch migration of vectors and hosts, presence of animal reservoir, and the impact of temperature. The improvements made to the existing models in the literature and the previous models developed by the authors resulted in a more nuanced and predictive model that yields potentially better results and lends itself more easily to detailed numerical exploration.

Unfortunately, the lack of field research, the very impetus that initially motivated our work, also prevents us from validating our model satisfactorily. Hence, the validation of the model is done qualitatively through a rigorous assessment of the results yielded by the model and compared to the generally applicable field research conclusions. The prevalence rates predicted by our model are within reasonable ranges of what is observed in reality. Furthermore, the behavior of lags in the impact of temperature on the vector populations and hosts prevalence rates are valid and consistent with the overall described behavior by the literature. The consistency of the results of the model with the general field research findings are especially impressive because the model constructed is built on first biological principles and does not assume any asymptotic behavior that would curb the results to fit the epidemiological findings. Hence, the authors feel confident about the results and believe that the model can be numerically analyzed to provide important epidemiological and entomological insight.

Analytical work previously done by the authors on the stability of the system but not specifically outlined in this thesis for the sake of brevity has shown that the vector population submodel is an example of a switched system[25] whose long-term behavior is regulated by temperature. In light of these findings we, in addition to the discussed revision and improvement of the existing vector population model and epidemiology submodels, also provide a significantly improved model for temperature behavior that is based on the existing model developed by Benth et al. The amended temperature model is an example of a temporal stochastic model that allows us to isolate and control for trend, seasonality, mean-reversion, and seasonally dependent randomized variance. We believe that the incorporation of such a comprehensive temperature model provides significant amount of value

as it lends itself nicely to analysis of different temperature components on the behavior of the disease. In our thesis we provide an example of such analysis by exploring the question of climate change. The impact of global warming on the behavior of the disease is a perfect example as there exists a vast amount of disagreement in the literature regarding how long-term climate change will occur. An expected rise in temperature can, for example occur simply through an increase in mean temperature values or it can, alternatively, occur only due to rise in minimum temperature extremes. Our temperature model allows us to uniquely address each possible scenario and in our thesis we focus on an example where the rise in temperature is a consequence of a trend change only. The numerical analysis performed indicates that a positive macro change in temperature trend has a small, yet not insignificant, beneficial impact on the prevalence rates.

Numerical analysis and sensitivity investigation previously done by the authors but, again for the purposes of maintaining focus, not specifically replicated in this thesis showed that the behavior of the disease is most sensitive to insect related parameters and quite insensitive to the epidemiological parameters not specifically related to insect population[25]. In this thesis we couple these findings with the entomological research which indicates that tsetse flies are unique among medically important vectors, with a series of genetic and demographic physiognomies that make them very susceptible to available control techniques[20]. Tsetse fly is unique as it does not lay eggs, but instead deposits mature larvae, which significantly results in low reproductive rates that in turn severely limit population growth rate. Furthermore, the tsetse fly also has low genetic variability, which reduces the probability of developing resistance to insecticides[20]. In light of these facts, we decided to focus significantly on the implementation, application, and optimization of vector control strategies. The three vector control strategies chose were trapping, insecticide treated cattle (ITC), and sterile insect technique (SIT).

Our numerical analysis showed that meticulous application of trapping will result in effective eradication if applied for a normally long period of time of one year. Our model, however, stresses the fact that effective eradication will only occur if trapping is implemented consistently and the area is protected from external invasion of new vectors. Analyzing the significant lag between effective eradication of the vector population and the eradication of the disease, we emphasize the importance of continuous regulation and control against re-invasion long after trapping has discontinued. Analyzing the optimization of implementation, we conclude that temperature

plays a small but significant factor in determining time efficiency of eradication, resulting in an up to approximately 4% change. This impact is partially mitigated by a long implementation period and slow-acting relative effect of trapping on vector population reduction. Further, we show that only a relatively small amount of area needs to be trapped on to achieve effective eradication, although the eradication period can initially be significantly reduced by trapping on a larger proportion of the overall region. If more than 45% of the area is populated with traps, our model predicts that vector eradication will take less than one year.

Eradication efficiency of ITC depends greatly on the relative proportion of cattle in the system. Through numerical analysis we showed that in order to effectively eradicate the disease in less than two years, approximately 10% of the domestic animal reservoir needs to consist of cattle. Quite remarkably, due to convexity of the relationship between eradication period and cattle proportion, in order to eradicate the disease in less than one year, approximately 16% of the domestic animal reservoir needs to be represented by cattle. Hence, our analysis concludes that even a small proportion of cattle in the system justifies the use of ITC as a viable control strategy. In fact, for the villages with a very high proportion of cattle our model concludes that ITC is a more time-efficient method than trapping. Time-efficiency analysis of ITC shows that temperature plays a more important role in determining the overall length of the eradication period, contributing to up to approximately 8% shorter time length of eradication if applied optimally. Our model suggest that in order to maximize the effectiveness of ITC, the method should be deployed in the early fall.

Consistent with the established literature, our numerical analysis shows that SIT does not normally lead to effective eradication of the vector. Nevertheless, based on our analysis, we state that SIT indeed provides significant value in its ability to utilize the unique biological characteristics of the vector to reduce vector population much faster than other techniques of vector control (trapping and ITC). Due to incomplete eradication, however, rate of prevalence reduction tends to be sluggish and smaller. Based on our conclusions we hence endorse the idea of coupling SIT with either trapping (or ITC) during its concluding stage of the implementation in order to achieve fast and effective results. Our optimization analysis shows that temperature plays a very significant role in determining the time efficiency of the control strategy in effectively eradicating the tsetse fly population. Because SIT is much faster acting, the role of temperature is amplified and can reduce the eradication period by up to approximately

25% if introduced at the right time in the year. Examining the relationship between resource-efficient and time-efficient eradication, we determine that the agents concerned with time efficiency (e.g. African governments) should focus more on increasing the number of males released at each interval, while the agents that are more capital-restricted (e.g. non-governmental organizations) should reduce the number of males released each time and instead increase the total number of releases. Our research also further supports previously made argument that relative time efficiency of SIT is proportional to the size of the region.

We conclude our investigation of control strategies by analyzing the employment and optimization of a non-vector control strategy active screening of the human population. Our analysis further supports the argument made by our sensitivity study, suggesting that vector control strategies are much better at disease eradication than the direct epidemiological strategies such as screening. We show that the implementation of screening cannot lead to long-term eradication of prevalence rates due to a significant impact of animal reservoir. This finding directly supports our previous analytical work done on the topic of host-specific reproduction numbers, which indicated that animal-specific reproduction number is large enough for the animal reservoir to maintain the infection even if the human population is removed from the system. Nevertheless, screening implementation does provide value that vector control strategies lack, as it provides an immediate relief to the infected human population. Due to time and funding constraints, screening cannot be performed very frequently and the question of optimal implementation is hence that much more important. Our numerical analysis of optimal timing to pilot the programme showed that the impact of screening can lead to up to approximately 25% change if implemented at the right time of the year. Our model suggests that the optimal timing for our specific region is in the spring.

Lastly, we explore, numerically, the impact of re-invasion and the importance of setting up vector population barriers. When re-invasion of flies is assumed, our standard application of control strategies does not lead to effective eradication - the relief, as expected, is only temporary. Our analysis emphazises the importance of setting up a barrier system when the re-invasion is plausible. Furthermore, the incorporation of invasion possibility into the model allows the future users of the model to control for this very realistic possibility when exploring the impact of the control strategies.

Moving forward, we remain firm in our belief that a primary purpose of applied mathematical modeling is to assist with the understanding of

reality. Hence, one of our hopes is that our model, incorporated with these control strategies, a stochastic temperature model, and an invasion module, is to be extended even further and developed into a user-friendly numerical tool that could help the agencies controlling the disease to make more informed and efficient decisions. With this idea in mind, our model was constructed so that it is both general in its function and specific in its results and can be applied to any local area as long as the suitable adjusting parameter values are available.

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