SEASONAL FLUCTUATION IN TSETSE FLY POPULATIONS AND HUMAN AFRICAN TRYPANOSOMIASIS: A MATHEMATICAL MODEL

T. MADSEN, D. I. WALLACE, N. ZUPAN

Dartmouth College
Hanover, NH, 03755, USA

Human African trypanosomiasis, commonly known as sleeping sickness, is a vector-borne disease endemic to Sub-Saharan Africa. An estimated 55 million people are at risk, and the World Health Organization classifies it as one of the world's neglected tropical diseases. We develop a model of the dynamics of one species of vector, *Glossina tachinoides*, which incorporates the impact of seasonal temperature fluctuation on the life cycle of the disease vector.

1. Introduction

Human African Trypanosomiasis (abbreviated HAT and commonly known as sleeping sickness) is an endemic public health threat to Sub-Saharan Africa. 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 known 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]. Infection by *T.b. gambiense* is fatal if left untreated [4]. 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 [5]. 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 [6]. 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 [7]. All trypanoso-

miases infect mammals exclusively [8].

Trypanosomiasis depends completely on the tsetse fly as a vector, with various stages taking place in both the mammalian host and the insect vector. Trypanosomes multiply in mammalian hosts, and are taken up when the fly takes a blood meal [2]. They then mature and migrate to the salivary glands of the fly, which permits transmission back to a mammalian host during a later blood meal [2].

These twenty to thirty fly species are highly localized, so the specific vector of HAT varies greatly from region to region [8]. Certain species of tsetse are more vulnerable than others to infection [8]. 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 [8]. Furthermore, different species of tsetse fly prefer different hosts [10]. The differences in behavior between tsetse flies of different regions make it difficult to develop general mathematical models of infection prevalence.

Despite the inherent challenges, one such general model of trypanosomiasis prevalence has been developed by Rogers [8]. This model is composed of a system of ordinary differential equations describing the prevalence rates of one species of trypanosome in one vector species and two host species (either human and domestic animal in the case of HAT or wild and domestic animal in the case of animal trypanosomiasis). Trypanosome transmission rates are considered to be a function of biting rates, the proportion of infected vectors and hosts, the proportion of bites resulting in transmission, and the ratio of vectors to hosts [5]. For simplicity, the model assumed that the populations of vector and hosts remained constant over time, as did other relevant factors such as temperature and humidity. Values for parameters that varied significantly by fly species (such as the duration of the tsetse feeding cycle and the average adult life expectancy) were calculated as a crude average. Consequently, this model is useful as a general model, but lacks the specificity to make strong predictions about any particular region or tsetse species. In this paper we develop a model of insect dynamics based on the behavior and lifecycle of a particular species of tsetse fly. Such a model may be coupled with the disease model of Rogers to give a better picture of disease dynamics.

2. Insect population submodel

A species of tsetse that lends itself to mathematical modeling is *Glossina tachinoides*, found in west and central Sub-Saharan Africa [10]. *G. tachinoides* is one of the major vectors of HAT [8]. It is a member of the *palpalis* group and is best suited to live in very humid areas such as rainforests, swamps, lakeshores, and gallery forests [10]. This species can live further north than most species of tsetse, so in some regions, it is the only vector of HAT [10]. *G. tachinoides* is only susceptible to *T. brucei* infection during its teneral stage (that is, it can only be infected during its first meal) [8]. The life span of adult females of this species is dependent on temperature and humidity, as are the durations of the pupal period and of the feeding cycle [10]. 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 [11]. This species was chosen as the point of reference for the model presented here.

The life cycle of tsetse is complicated and rather unique [10]. Adult females mate only once during their lifetime, although males can mate more than once. 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. 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, humidity, and temperature [10]. 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 [8]. The first meal is very important as this food is used to develop the flight muscles in the thorax, which are undeveloped at emergence [10]. Flies are vulnerable to infection by *T. brucei* in this weak state, and develop immunity after their first blood meal [8].

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 [10].

2.1. *Insect Model Equations*

We assume that every adult female fly mates successfully, independent of the male population.

We do not assume that temperature is constant. However, we assume that its effect on parameters is linear when the effect is increasing monotonic in the temperature range of 19 to 33 degrees. If the effect is optimal somewhere in that range and declines otherwise, we model it with a quadratic. This assumption allows a crude match to known parameters at various temperatures in a reasonable range around the average.

Most population models rely on a carrying capacity to bound population growth. 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 [12] [13] [14] and there appear to be plenty of mammals to provide blood meals. Production of pupae is so small that no constraint seems relevant there. Therefore we do not assume any *apriori* bound on fly populations, and instead explore the role of temperature as a controlling factor.

Equations 1-4 below describe the dynamics of the fly population ($P =$ pupae, $R =$ teneral, $F =$ female, $M =$ male).

The rate of change in the pupa population is given by the rate of pupa deposition less the rate of maturation and the death rate.

$$P' = I^{-1}F - QL^{-1}rP - VP \tag{1}$$

The rate of change in the teneral population is given by the rate of maturation of pupae less the rate of maturation of tenerals and the death rate.

$$R' = QL^{-1}rP - CE^{-1}rR - BHrR \tag{2}$$

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

$$F' = .5CE^{-1}rR - (S(r - DW^{-1})^2 + A^{-1})F \tag{3}$$

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

$$M' = .5CE^{-1}rR - N^{-1}M \tag{4}$$

Values of all variables and constants are summarized in Table 1 below.

Table 1. Parameters for the insect submodel

Notation	Value	Units	Description	Source
A	90	*days*	maximum life expectancy of female fly	[10]
B	.97	-	teneral death temperature correction	[10]
C	1.12	-	feeding cycle temperature correction	[10]
D	25	Celsius	temperature for optimal female life expectancy	[10]
E	4	*days*	average duration of fly feeding cycle	[8]
F	variable	number	female fly population, initially 3000	-
H	.14	$days^{-1}$	average teneral death rate	[10]
I	9	*days*	duration of larval period	[10]
L	26	*days*	duration of pupal period	[10]
M	variable	number	male fly population, initially 2000	-
N	21	*days*	average life expectancy of male fly	[10]
P	variable	number	pupal population, initially 5000	-
Q	1.02	-	pupal period temperature dependency correction	[10]
R	variable	number	teneral population, initially 1000	-
S	.292	-	female life expectancy temperature correction	[10]
T	variable	Celsius	temperature, initially 25C (January 1st)	[15]
V	.04	-	average pupal death rate	[10]
W	29	Celsius	average yearly temperature	[15]

2.2. *Explanation of Equations*

Pupa population

The number of pupae deposited daily depends on the number of adult females and the rate at which the adult females are depositing pupae. On average, an adult female deposits a pupa every ten days and has a larval period of about 9 days [10]. We estimate that on a given day, the number of pupae deposited is one-ninth the number of adult females. Tsetse flies breed continuously, not in waves or cycles, so this is not an invalid assumption [16]. Well call this nine-day period the larval period, and denote its duration by I. It is worth noting that using a 10 day period does not significantly alter any of the results described below.

The number of pupae emerging into tenerals daily depends on atmospheric temperature. On average, the length of the so-called pupal period

(L) is about thirty days. However, as temperatures rise, the pupa develops more quickly. At 19C, the pupal period lasts about thirty-eight days, and at 33C, the period only lasts twenty-three days [10]. To model this behavior, we assumed that the number of daily emergences from puparia was the product of the number of pupae, the average rate of daily emergence (estimated as the inverse of the length of the pupal period, 1/L), the ratio of the current temperature to the yearly average temperature (T/W, which we'll abbreviate by r), and a correction factor Q that quantifies the impact of the temperature ratio on the length of the pupal period. Q was estimated by comparing the average pupal period and annual temperature to the known pupal period-temperature data given above, and averaging the size of the necessary correction factor for each data point. This method is highly approximate, but does provide a loose estimate of the dependence of average pupal period duration on temperature. The value of L (or equivalently, Q) was adjusted to fit approximately the two endpoints at 19 and 33 degrees.

The daily death rate of pupae is unfortunately very difficult to estimate. Pupae can die in many ways - parasites, predators, flooding, dehydration and freezing all appear to be major sources of pupal death, and little is known about their relative importance [10]. Some data indicates that pupal death is correlated with temperature [10]. At the end of the four-month long rainy season, about half of pupae collected are dead, but at other times, nearly all pupae found will give rise to adult flies [10]. Since this data is collected seasonally, we estimate that if about eight percent of twelve consecutive ten-day generations of pupae die, then at the end of the season, we'd expect to find about as many dead pupae as living ones. So we estimate that during such a rainy season, approximately eight percent of pupae die. At average temperatures, it appears that no pupae die, and there is little data to support any particular model of intermediate conditions. An average relative death rate of $V = .04$ was therefore used.

Teneral population

To estimate the size of teneral population, we assumed that only three factors affected its size: emergence from puparia, death of tenerals, and emergence into adults.

Of course, the pupal emergence term is given above, and serves as the gain term for tenerals in the same way it serves as the loss term for pupae.

The daily number of tenerals emerging into adults depends on the number of tenerals and how frequently they eat, which turns out to also be temperature-dependent [10]. High temperatures reduce the amount of time that flies can live without a blood meal, and low temperatures have the op-

posite effect [10]. Other species of tsetse (not *G. tachinoides*), for which more data is available, demonstrate about a 20% fluctuation in the duration of their feeding cycle at extreme temperatures [10]. We assume that the daily rate of emergence into adults is dependent on the product of the inverse of the average length of the feeding cycle (1/E, also the average length of the teneral period), the ratio of the actual temperature to the average temperature, and a correction factor C that reflects the significance of temperature in determining the length of the feeding cycle. Note that this term takes precisely the same form as the teneral emergence term in the differential equation for P. This correction factor was calculated in the same way as Q. We assume a similar dependence on temperature for the death rate of tenerals.

With the constants chosen for this model, at 19 degrees Celsius the amount of time spent in the teneral stage is 5.3 days and at 33 degrees it is about 3 days. These values bracket an intermediate value of $E = 4$, as suggested by Rogers [8].

Female adult population

We assume that the size of the female population depends only on emergence by tenerals and death. Only half of emerging tenerals become adult females. The death rate of adult females is believed to be temperature dependent [10]. During the dry season, the average female life expectancy of *G. tachinoides* is one month; in the rainy season, the life expectancy is three months [10]. To model this temperature dependence, we assume that the rate of adult female death is the sum of the inverse of the optimal life expectancy (1/A) and a correction factor that increases at the temperature varies from optimal (D), modeled as a quadratic function of the ratio of that difference to mean annual temperature, W. A correction factor, S, adjusts the quadratic so that endpoints approximate observations on the interval from 19 to 33 degrees Celsius.

Male adult population

The growth of the male population is identical to that of the female population, except that the male life expectancy is not temperature-dependent [10], so the temperature-dependent life expectancy term in the above equation can be replaced with a constant 1/N term, where N is the average life expectancy of male tsetse.

Table 1 summarizes the parameters used in the insect population equations, gives default parameters for numerical experiments and sources from which these data were taken.

2.3. *Temperature Model*

It is clear that fly populations fluctuate seasonally, both in size and in density [8]. Unfortunately, it is very difficult to estimate the number of tsetse living in an area at a given time. The best metric is given by their so-called 'apparent density', which is measured by the number of non-teneral males caught in traps per day. This metric is flawed, though, as a high apparent density may reflect a hungry population instead of a large population [10].

The duration of almost every stage in the tsetse cycle is temperature dependent [10]. We defined a parametric temperature function (T) using average daily temperature data collected at Ouagadougou Airport in Ouagadougou, Burkina Faso [15], where the average annual temperature is 29 C. Clearly, not all years are the same, but the model was run with periodic temperatures for several years to get a picture of its behavior over time.

3. Analysis of model

The insect submodel is a homogeneous linear model. It has only one equilibrium, with all populations zero. If we set $q = Q/L, c = C/E, d = D/W, r = T/W$ the system may be represented by the following matrix:

$$\begin{pmatrix} qr - v & 0 & I^{-1} & 0 \\ qr & cr - BHr & 0 & 0 \\ 0 & .5cr & -(A^{-1} + S(r-d)^2) & 0 \\ 0 & .5cr & 0 & -N^{-1} \end{pmatrix}. \tag{5}$$

All of the entries in this matrix are constant except r, which varies above and below 1. In the following discussion we will treat r as a constant and look at the behavior of the system over a range of possible values of r.

The characteristic polynomial for the system is given in Equations 6 and 7.

$$P(\lambda) = (-\lambda - N^{-1})Q(\lambda) \tag{6}$$

where

$$Q(\lambda) = (-\lambda-(qr+v))(-\lambda-(cr+BHr))(-\lambda-(S(r-d)^2+A^{-1}))+(2I)^{-1}qcr^2 \tag{7}$$

The cubic factor is a polynomial with three negative roots plus a quantity added at the end. This small quantity has the potential effect of in-

creasing the root nearest zero to a positive number, thereby creating an unstable system.

3.1. *Instability of the model with constant temperature D*

The characteristic polynomial for the system factors into a linear term and a cubic.

$$P(\lambda) = (-\lambda - N^{-1})(-\lambda^3 - \alpha\lambda^2 - \beta\lambda + \delta) \tag{8}$$

The values of α, β, and δ all vary with r. However α and β are always positive. Thus, by DesCartes' rule of sign, the system will have a positive root if δ is positive, and in that case will be unstable. It is easy to see that δ is given by

$$\delta(r) = -(qr + v)(cr + BHr)(S(r - d)^2 + A^{-1}) + (2I)^{-1}qcr^2 \tag{9}$$

If the temperature is set to the optimize the lifespan of the female, then $r = d$. With other constants at default values, this gives a positive value for δ, and instability of the system.

3.2. *Sufficient insect death leads to stability*

Because the diagonal entries of the matrix in Equation 6 are negative, a corollary of Gerschgorin's Circle Theorem [17] guarantees stability when the column sums are negative. The only column sum which is not necessarily negative is $I^{-1} - (S(r-d)^2 + A^{-1})$. At default parameters this expression is negative for $r < .25$ and $r > 1.44$, guaranteeing stability at those (extreme) temperatures. The theorem does not preclude the possibility of stability in a more reasonable range as well.

3.3. *Variable temperature as a switched system*

It is worth noting that the system exhibits both stable and unstable behavior depending on the temperature, with stability at both extreme temperatures. In this case the system is a continuous example of a "switched system" [18] whose long term behavior goes to some intermediate value. This model shows the long term behavior of a population which, under some conditions, experiences unconstrained growth. This growth is tempered by temperature conditions which, if in place long enough, would eliminate the population entirely.

4. Numerical results of insect submodel

Equations 1-4 were run using Matlab's ODE45 solver. The sensitivity diagrams of Figure 3 were produced from Matlab output using Excel. All figures were postprocessed using Adobe Photoshop.

Figure 1 shows the results of the population model in Equations 1-4, coupled with the temperature model described in Equation 5.

Figure 1. The top graph shows all four populations over an 1800 day interval. The lower graph shows temperature data input for that period.

As the analysis suggests, the fly population is controlled effectively by the oscillating temperatures. When the temperature rises to about 32 degrees Celsius the female fly population begins to decline, and continues to do so until temperatures drop to around 29 degrees. Because this model is strictly periodic in temperature, the overall population must either decline or grow. For these parameter choices it declines, although very slowly.

4.1. *Rogers' model revisited*

The model Rogers proposed [8] assumes one vector population and two host populations. The full model is described in that paper. Here, for simplicity, we assume only a human host population. The fly populations assumed to be constant by Rogers we take to be varying, and use the model developed here as the source for those varying populations over time. Figure 2 shows the resulting variation in human disease prevalence, along with the temperature variation during the same period.

Figure 2. Rogers' model is coupled with the insect dynamics developed in this paper. The top graph shows percent of humans infected and percent of vectors infected (negligible by comparison) over the same time period as in Figure 1. The lower graph shows the temperature input during that period.

There are a few things worth noting here. First of all, the peaks of prevalence coincide with high temperatures. This is a sum of two time lags. There is a lag between when the temperature drops to optimal for the insect vector and when its populations peak, visible in Figure1. There is then a second lag between the rise in insect population and the peak of infection.

The second thing we note is that the oscillations are not large. Rogers assumes a relatively slow return rate from the infected to the susceptible pool. If this rate were improved through aggressive medical interventions, the picture could be different.

Four reasons for seasonal fluctuation of vector borne disease have been proposed, one of which is variation in the population of the vectors themselves [19]. Observed seasonal fluctuations of tsetse are documented in Kenya [14], Burkina Faso [12], and Ethiopia [13]. Accurate measurements of these fluctuations are difficult. Generally cattle are used as bait and the result is some measurement of both the density of flies and how hungry they are. Comparison with trapping data in the Burkina Faso study [12] does show a drop in fly density after temperature peaks, as does our model in Figure 1.

5. Sensitivity of the model

A sensitivity analysis was conducted on both the full model and the insect submodel.

For each quantity, the outcome analyzed is the average of the high and the low values on the interval from t=500 to t=1800. The sensitivity analysis is computed by fixing all the parameters in the model but one which is varied by +/- 10% (submodel) or +/- 1% (full model). The resulting change in each outcome is recorded as a percent of the base value, and parameters are ordered by size effect. The results are summarized in Figure 3, which shows the sensitivity of the female fly population on the left and human disease incidence on the right. All of the fly populations behaved similarly, so only this one is displayed.

Figure 3. On the left parameters for the insect model are ordered by the size of their effect on the female fly population, as described above. On the right the same is done for the insect model coupled with a version of Rogers' disease model.

The parameter D, which represents the optimal temperature for prolonging the life expectancy of female flies, has by far the largest effect, changing the female fly population by a thousand percent and the human disease prevalence by seventy five percent. The parameters with the largest size effect in the human disease model all come from the population model developed in this paper. That is, variation in insect population dynam-

ics has a bigger effect on disease prevalence than the disease parameters themselves.

Parameters listed in lower case letters occur only in the model of human disease prevalence. The one to have the largest effect in our sensitivity analysis was a, which represents the proportion of of blood meals taken from humans (as opposed to other mammals). The default value for this parameter was twelve percent. This, and all default parameters for the disease model, are as in Rogers' original work [8]. The next two largest effects are from m, which represents the total human population, and b, the probability of a bite leading to infection.

6. Summary of results

In this paper we construct a temperature dependent model of tsetse fly population dynamics and couple it with a version of Rogers' epidemiology model for Human African Trypanosomiasis. Analysis and numerical investigation of the insect model yields the following insights.

(1) The temperature dependent insect population model has oscillating behavior with time lags qualitatively similar to observed data [12].
(2) The model varies between stable and unstable states, with stability at the extreme values of temperature and instability at intermediate values. In this way temperature controls the insect population.
(3) The model is an example of a continuously switched system, in the sense of control theory [18].
(4) Behavior of both the insect model and the coupled disease model is most sensitive to insect related parameters, and especially the temperature that optimizes the female life span.
(5) The coupled disease model was relatively insensitive to the parameters not associated with the insect submodel.

These results suggest that control of the fly is the key to control of this disease. It also suggests that climate change will play a big role in spread of trypanosomiasis. Finally, the model shows that a better understanding of the particular response of tsetse to temperature is key to predicting outbreaks, as the model is very sensitive to the parameters related to temperature.

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