Journal of Biological Systems, Vol. 4, No. 4 (1996) 459–477

A COMPARTMENTAL MODEL OF SLEEPING SICKNESS IN CENTRAL AFRICA

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Received 24 February 1995
Revised 21 May 1996

ABSTRACT

We present a five-variable compartmental model for the spread of *Trypanosoma brucei gambiense*, the parasite responsible for the transmission (through tsetse flies) of sleeping sickness in Central Africa. The model's equilibrium points depend on two "summary parameters": g_r, the proportion removed among human infectives, and R_0, the basic reproduction rate. Stability results are obtained for the origin but not for other equilibrium points. A two-variable simplified version of the model is presented and the stability of all its equilibrium points can be investigated analytically. Both models are applied to the Niari focus of Central Africa and used to test the impact of a vector control strategy. The models' results are in agreement with the extinction of the epidemic that was brought about by a fifty percent decrease in vector density.

Keywords: Epidemiology, compartmental model, sleeping sickness, differential equations, stability.

1. Introduction

During the last hundred years Africa was struck by three sleeping sickness epidemics: one at the end of the 19th century; one at the beginning of the 20th century [22], and a third since the mid 1960s, first in the Congo and Zaire, then in other Central African countries [18].

Mathematical models with density-dependence have been proposed in order to help better understand the dynamics of vector-borne diseases such as malaria [2,4,7,21], among others. Sleeping sickness (or trypanosomiasis) is a disease that affects both animals and humans and is transmitted by the tsetse fly. However, its epidemiology is still not well understood [3,6,8,15,25,30,31]. A causal model of the human disease was described by De Muynck *et al.* [6] and a few models have been proposed for the spread of animal trypanosomiasis [16,23].

Rogers' model of Gambian sleeping sickness is one of the few models available on human trypanosomiasis but it has met with mixed results. Indeed, when fitted using data on age-prevalence curves, the model yields implausibly low tsetse biting

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rates on humans ([27–29], also see Gettinby [10] for a review of trypanosomiasis modeling).

Our goal is to contribute to a better understanding of the dynamics of sleeping sickness by proposing a compartmental model for *Trypanosoma brucei gambiense* in Central Africa. We will assume that only humans are reservoirs for the parasite, unlike Rogers [27,29] who also considers animal reservoirs. We make this simplifying assumption because low prevalence rates of human parasites in animals of Central Africa suggest that the animal reservoir is indeed a negligible factor in the transmission of Gambian trypanosomiasis [17,26]. Also, the large epidemic that devastated Central Africa at the beginning of the century could not have been brought under control by detection and treatment methods if animal reservoirs were a significant factor.

In Sec. 2 we will describe the model and analyze its equilibria. In Sec. 3 we will introduce a simplified version of the model and give a result concerning the stability of its equilibrium points. Section 4 presents a realistic illustration of the model with data from a Central African focus studied by one of the authors. Results are discussed and summarized in Sec. 5.

2. The Model

2.1. *Description*

We will consider an "epidemiologic unit" made of an isolated village and a closed population of vectors. (This simplifying assumption is valid in savanna areas and may be less valid in forest areas where three are no clear geographic boundaries for the fly populations.) We thus assume a closed system characterized by constant vector and human populations V and H. When they die vectors and humans are replaced by new susceptibles through births.

In addition to the susceptibles, our model will consist of two compartments for the infected vector population and three for the infected humans hosts (Fig. 1).

1. Infected vectors first go through an incubation period, followed by a period of active infection, followed by death. Vectors can infect humans only during the active infection period.
2. Infected humans first incubate, then enter the compartment of asymptomatic carriers who can transmit the parasite through fly bites. When they enter the second phase (meningo-encephalitic phase) of the disease or are removed to be treated then they enter the removed compartment of individuals who can no longer transmit the parasite. Thereafter they either die or re-enter the susceptible population when they are cured. All humans except the removed ones are at risk of being bitten by a fly (and can be infected by or transmit *Trypanosoma brucei gambiense*).

The model is a continuous one and consists of the parameters given below. (Δt is a very short period of time, and the unit of time will be taken as three days which is the average time between blood meals.)

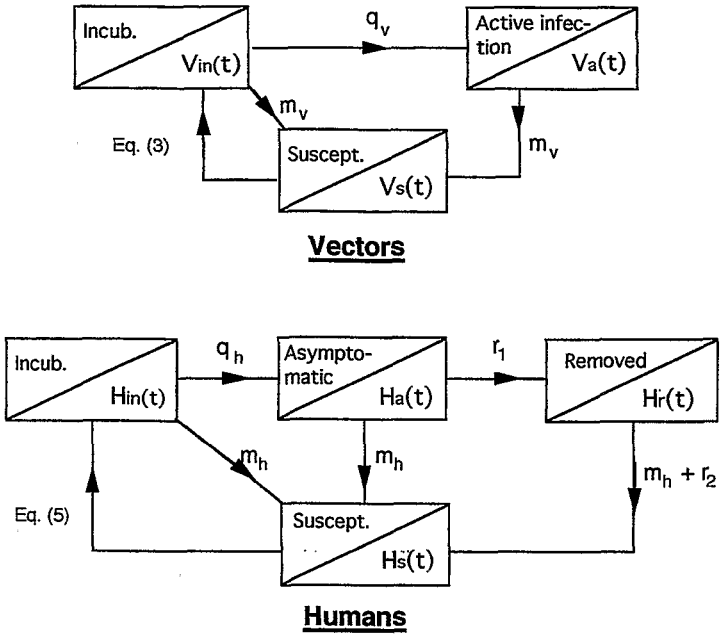


Fig. 1. Compartments of the model.

2.2. *Parameters*

1. $\tau_1 \Delta t$ = probability that a vector will have a blood meal on a human during a time interval of length Δt. (When it is small the parameter τ_1 is approximately equal to the probability that a fly will have a blood meal during a three-day period since the unit of time is three days.)
2. τ_2 = probability that a susceptible vector eventually becomes infected after biting an infected human; τ_2 reflects the "intrinsic vectorial capacity" as well as an average probability of infection that ignores each patient's periodic parasitemic fluctuations (which are caused by the parasite's antigenic variations).
3. τ_3 = probability that a susceptible human bitten by an infected fly will become sick. (τ_3 is the "human susceptibility".)
4. q_v, q_h = rates at which vectors and hosts leave the incubating stage; $1/q_v$ and $1/q_h$ are therefore the durations of the incubation periods.
5. r_1 = transition rate between the asymptomatic and the removed compartments. This transition reflects the natural history of the disease for infected individuals who move from the first asymptomatic stage to the meningo-encephalitic stage when they can no longer transmit the parasite. This transition also reflects the detection of sick individuals when they are removed to be treated.
6. r_2 = transition rate from the removed compartment back into the susceptible compartment. This rate reflects both the recovery of treated individuals and

the mortality induced by the disease. Although both transitions are of a very different nature from the individual's point of view, they are mathematically equivalent because the system is assumed closed. A death compensated by an uninfected birth (when there is no vertical transmission [19]) is equivalent to a recovery. This equivalence is also made possible by the fact that the human age-structure is ignored in the model.

7. m_v, m_h = natural death rates for the two species. Birth rates will be equal to death rates since the populations are assumed constant and closed. We will make use of the fact that the population of flies aged less than three days is then approximately Vm_v.

2.3. *Variables and Equations*

$V_s(t), V_{in}(t), V_a(t)$ = susceptible, incubating, and actively infected vectors at time t:

$$V = V_s(t) + V_{in}(t) + V_a(t), \qquad \text{for all } t. \tag{1}$$

$H_s(t), H_{in}(t), H_a(t), H_r(t)$ = susceptible, incubating, asymptomatic, and removed humans at time t:

$$H = H_s(t) + H_{in}(t) + H_a(t) + H_r(t), \qquad \text{for all } t. \tag{2}$$

There are seven variables which can immediately be reduced to five if we use Eqs. (1) and (2) to express the susceptible populations $V_s(t)$ and $H_s(t)$ in terms of the other variables. With explanations following, we then have five equations that give the populations at time $t + \Delta t$ as functions of the same populations at time t:

$$V_{in}(t+\Delta t) = Vm_v\tau_1(\Delta t)\tau_2 \frac{H_a(t)}{H - H_r(t)} + V_{in}(t)(1 - q_v\Delta t - m_v\Delta t), \tag{3}$$

$$V_a(t+\Delta t) = V_{in}(t)q_v\Delta t + V_a(t)(1 - m_v\Delta t), \tag{4}$$

$$H_{in}(t+\Delta t) = \tau_1(\Delta t)\tau_3 V_a(t)\left(\frac{H - H_{in}(t) - H_a(t) - H_r(t)}{H - H_r(t)}\right) + H_{in}(t)(1 - q_h\Delta t - m_h\Delta t), \tag{5}$$

$$H_a(t+\Delta t) = H_{in}(t)q_h\Delta t + H_a(t)(1 - r_1\Delta t - m_h\Delta t), \tag{6}$$

$$H_r(t+\Delta t) = H_a(t)r_1\Delta t + H_r(t)(1 - m_h\Delta t - r_2\Delta t). \tag{7}$$

Equation (3): Because flies can become infected only during their first blood meal (while they are in the first three-day age group) the number of flies at risk of becoming infected (i.e. of entering the incubating stage) is approximately Vm_v (since the number of flies in the first three-day age-group is approximately Vm_v). In order to become infected, any one of the Vm_v flies must first have a blood meal in the time interval Δt (probability $= \tau_1\Delta t$); then it must bite an asymptomatic carrier. (There are $H_a(t)$ such carriers and the probability of this happening is

$H_a(t)/[H - H_r(t)]$ because only $H - H_r(t)$ humans are at risk of being bitten.) Finally, the potentially infectious meal must actually lead to an infection (probability $= \tau_2$), hence the first term on the right-hand side of Eq. (3). The second term reflects losses to the asymptotic compartment and death.

Equation (4): Expresses losses (due to death) and gains (due to new infections) among the actively infected vectors.

Equation (5): Newly infected humans (entering the incubating stage) are those infected by the $V_a(t)$ actively infected flies. These flies have a blood meal with probability $\tau_1 \Delta t$; this blood meal is on a susceptible human with probability $H_s(t)/(H - H_r(t))$ with $H_s(t)$ obtained through Eq. (2). The probability that the bite will lead to infection is τ_3.

Equations (6) and (7) are routine balance equations.

The two equations that give $V_s(t + \Delta t)$ and $H_s(t + \Delta t)$ are:

$$V_s(t + \Delta t) = (V_{in}(t) + V_a(t))m_v \Delta t + V_s(t) - V m_v \tau_1(\Delta t)\tau_2 \frac{H_a(t)}{H - H_r(t)}, \tag{8}$$

$$H_s(t + \Delta t) = (H_{in}(t) + H_a(t) + H_r(t))m_h \Delta t + H_r(t) r_2 \Delta t + H_s(t) - \tau_1(\Delta t)\tau_3 V_a(t)\left(\frac{H - H_{in}(t) - H_a(t) - H_r(t)}{H - H_r(t)}\right). \tag{9}$$

As indicated above, these equations will not be necessary in the analysis because they are redundant: Eq. (8) = Eq. (1) − Eq. (3) − Eq. (4) and Eq. (9) = Eq. (2) − Eq. (5) − Eq. (6) − Eq. (7).

Equations (8) and (9) express the fact that there is no vertical transmission of sleeping sickness for either species since deaths are compensated by births into the susceptible compartment only. These equations also show that as a simplifying assumption we have postulated that vector birth and death rates were the same in all compartments which implies no mortality induced by the disease and no change in fertility for the tsetse population.

2.4. *Stability Analysis*

We now express the system of equations in terms of the proportions $v_{in}(t) = V_{in}(t)/V, v_a(t) = V_a(t)/V, h_{in}(t) = H_{in}(t)/H, h_a(t) = H_a(t)/H, h_r(t) = H_r(t)/H$ (with $v_s(t) = V_s(t)/V$ and $h_s(t) = H_s(t)/H$). When we let $\Delta t \to 0$ the Eqs. (3)–(7) then yield the following system of differential equations:

$$\frac{dv_{in}(t)}{dt} = m_v \tau_1 \tau_2 \frac{h_a(t)}{1 - h_r(t)} - v_{in}(t)(q_v + m_v), \tag{10}$$

$$\frac{dv_a(t)}{dt} = v_{in}(t) q_v - v_a(t) m_v, \tag{11}$$

$$\frac{dh_{in}(t)}{dt} = \tau_1\tau_3 v_a(t)\frac{V}{H}\left(\frac{1-h_{in}(t)-h_a(t)-h_r(t)}{1-h_r(t)}\right) - h_{in}(t)(q_h+m_h)\,, \tag{12}$$

$$\frac{dh_a(t)}{dt} = h_{in}(t)q_h - h_a(t)(r_1+m_h)\,, \tag{13}$$

$$\frac{dh_r(t)}{dt} = h_a(t)r_1 - h_r(t)(m_h+r_2)\,. \tag{14}$$

The equilibrium values $(v_{in}^*, v_a^*, h_{in}^*, h_a^*, h_r^*)$ will be the values of the variables $v_{in}(t), v_a(t), h_{in}(t), h_a(t), h_r(t)$ for which both sides of Eqs. (10)–(14) are equal to zero. We note that $(v_{in}^*, v_a^*, h_{in}^*, h_a^*, h_r^*) = (0,0,0,0,0)$ is always a trivial equilibrium point.

We define the total infected populations:

$$v_{INF}(t) = v_{in}(t) + v_a(t), \quad h_{INF}(t) = h_{in}(t) + h_a(t) + h_r(t) \tag{15}$$

and the corresponding equilibrium values:

$$v_{INF}^* = v_{in}^* + v_a^*,\ h_{INF}^* = h_{in}^* + h_a^* + h_r^*\,. \tag{16}$$

If we define $s_1 = q_h/(r_1+m_h)$ and $s_2 = r_1/(m_h+r_2)$, and let

$$g_{in} = \frac{1}{1+s_1+s_1s_2}, \quad g_a = \frac{s_1}{1+s_1+s_1s_2}, \quad g_r = \frac{s_1s_2}{1+s_1+s_1s_2} \tag{17}$$

then Eqs. (13) and (14) show that the human equilibrium values, when they exist, satisfy

$$h_{in}^* = g_{in}h_{INF}^*, \quad h_a^* = g_a h_{INF}^*, \quad h_r^* = g_r h_{INF}^*\,. \tag{18}$$

The parameters g_{in}, g_a, and g_r thus represent the equilibrium proportions, among infected humans, in each compartment.

Similarly, if we define

$$k_{in} = (m_v/q_v)/(1+m_v/q_v),\ k_a = 1/(1+m_v/q_v) \tag{19}$$

then

$$v_{in}^* = k_{in}v_{INF}^*,\ v_a^* = k_a v_{INF}^* = \frac{k_a}{k_{in}}v_{in}^* \tag{20}$$

and k_{in}, k_a are the equilibrium proportions among infected vectors. We also define the quantity

$$R_0 = \frac{\tau_1^2\tau_2\tau_3 - q_h - V}{(r_1+m_h)(m_h+q_h)H}\,\frac{q_v}{(m_v+q_v)} \tag{21}$$

which is the basic reproduction rate (BRR) of the epidemic. Indeed the quantity $R_1 = \tau_1\tau_2 q_h V m_v/[(r_1+m_h)(m_h+q_h)H]$ is the number of flies infected by one infected human and $R_2 = \tau_1\tau_3 q_v/[m_v(m_v+q_v)]$ is the number of humans each infected fly will infect in turn. The product R_1R_2 is R_0, the BRR, which is the

number of humans one newly infected human will infect (via the vectors) during the course of the disease.

A first result shows that equilibrium points depend only on the values of the two "summary parameters" g_r and R_0. The theorem will hinge on a quadratic equation of which h^*_{INF} is a solution, from which other equilibrium values can be calculated using Eqs. (10)–(14) and Eqs. (18) and (20). Indeed, Eqs. (10)–(14) set equal to 0 show that once the trivial equilibrium $h^*_{INF} = 0$ has been factored out, h^*_{INF} is the root of the following quadratic equation:

$$h^2 g_r^2 - (2g_r - R_0)h + 1 - R_0 = 0\,. \tag{22}$$

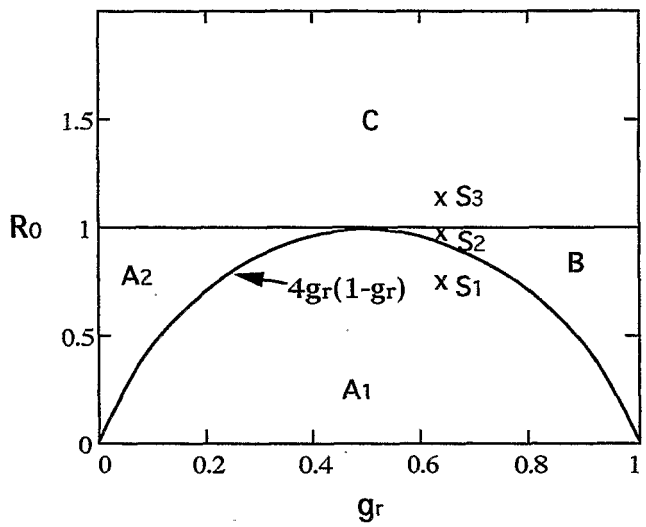


Fig. 2. Number of roots of Eq. (22) as a function of (g_r, R_0) [C: 2 roots of opposite signs; B: 2 positive roots; A_1: 2 complex roots; A_2: 2 negative roots]. Empirical values (S_1, S_2, S_3) for the Niari focus of Sec. 4 are also plotted.

Theorem 1. When $R_0 < 1$ the origin is a stable equilibrium point. If in addition $g_r < 0.5$ or $R_0 < 4g_r(1-g_r)$ (regions A_1 and A_2 of Fig. 2 in the (g_r, R_0) plane) then the origin is the only equilibrium point. If $g_r > 0.5$ and $R_0 > 4g_r(1-g_r)$ (region B) then there are two additional positive equilibrium points $(v_{in}^{*(1)}, v_a^{*(1)}, h_{in}^{*(1)}, h_a^{*(1)}, h_r^{*(1)}$ and $(v_{in}^{*(2)}, v_a^{*(2)}, h_{in}^{*(2)}, h_a^{*(2)}, h_r^{*(2)})$ with corresponding infection prevalences of humans $h_{INF}^{*(1)}$ and $h_{INF}^{*(2)}$ that are the roots of Eq. (22):

$$h_{INF}^{*(1)} = \frac{2g_r - R_0 - \sqrt{R_0}\sqrt{R_0 + 4g_r(g_r - 1)}}{2g_r^2}\,, \tag{23}$$

$$h_{INF}^{*(2)} = \frac{2g_r - R_0 + \sqrt{R_0}\sqrt{R_0 + 4g_r(g_r - 1)}}{2g_r^2}\,. \tag{24}$$

When $R_0 > 1$ (region C) the origin is unstable and there is one other positive equilibrium point $h^{*(2)}_{INF}$ given by Eq. (24).

Conjecture: When there are two positive solutions $h^{*(1)}_{INF}$ and $h^{*(2)}_{INF}$ of Eq. (22) (region B), then $h^{*(1)}_{INF}$ is unstable and $h^{*(2)}_{INF}$ is stable. When $R_0 > 1$ (region C) the positive solution $h^{*(2)}_{INF}$ is stable.

Proof. See Appendix 1.

The conjecture is based on a result obtained for a simplified version of this model that has only two variables. This is the subject of the next section.

3. The Simplified Two-Variable Model

When Eqs. (10) and (11) are added, the proportion of infected flies $v_{INF}(t)$ (see Eq. (15)) satisfies the differential equation:

$$\frac{dv_{INF}(t)}{dt} = m_v \tau_1 \tau_2 \frac{h_a(t)}{1 - h_r(t)} - v_{INF}(t) \cdot m_v \,. \tag{25}$$

Similarly, when Eqs. (12)–(14) are added we obtain

$$\frac{dh_{INF}(t)}{dt} = \tau_1 \tau_3 v_a(t) \frac{V}{H} \left(\frac{1 - h_{in}(t) - h_a(t) - h_r(t)}{1 - h_r(t)} \right) - h_{INF}(t) m_h - h_r(t) r_2 \,. \tag{26}$$

These equations suggest the possibility of a simplified model with only the two variables $v_{INF}(t)$ and $h_{INF}(t)$, i.e., the total proportions infected; $1 - v_{INF}(t)$ and $1 - h_{INF}(t)$ are then the susceptible proportions. The simplifying assumption we will make is that the proportions in each infective "sub-compartment" are constant fractions of the total infected populations, i.e., for all t, there are positive numbers g'_{in}, g'_a, and g'_r summing to 1 and k'_{in} and k'_a summing to 1 such that

$$h'_{in}(t) = g'_{in} h'_{INF}(t); \; h'_a(t) = g'_a h'_{INF}(t); \; h'_r(t) = g'_r h'_{INF}(t) \tag{27}$$

$$v'_{in}(t) = k'_{in} v'_{INF}(t); \; v_a(t) = k'_a v'_{INF}(t) \tag{28}$$

where primes are to emphasize that this is a different model. With these assumptions the variables with the subscripts "a", "r", "in" disappear in Eqs. (25) and (26), and these two equations yield a system of differential equations in the renamed variables $v'_{INF}(t)$ and $h'_{INF}(t)$ only:

$$\frac{dv'_{INF}(t)}{dt} = m_v \tau_1 \tau_2 \frac{h'_{INF}(t) g'_a}{1 - h'_{INF}(t) g'_r} - v'_{INF}(t) \cdot m_v \,, \tag{29}$$

$$\frac{dh'_{INF}(t)}{dt} = \tau_1 \tau_3 v'_{INF}(t) k'_a \frac{V}{H} \left(\frac{1 - h'_{INF}(t)}{1 - h'_{INF}(t) g'_r} \right) - h'_{INF}(t)(m_h + g_r r_2) \,. \tag{30}$$

The basic reproduction rate for this model is

$$R'_0 = \frac{\tau_1^2 \tau_2 g'_a \tau_3 k'_a V}{(m_h + g'_r r_2) H} \,. \tag{31}$$

The parameters g'_{in}, g'_a, g'_r, k'_{in} and k'_a may or may not be equal to their unprimed counterparts of Eq. (17) and Eq. (19). When they are, then at all times the structure of the infected populations remains equal to the equilibrium structure of the original model. In the neighborhood of an equilibrium point this simplified model is then equivalent to the original model and $R_0 = R'_0$ (we will say that both models are then "asymptotically equivalent"). The following theorem is analogous to Theorem 1, except that the result that was only conjectured in the original model is proven for the simplified version. This theorem is true whether or not g'_{in}, g'_a, g'_r, k'_{in} and k'_a are equal to their unprimed counterparts in the original model.

Theorem 2. For the simplified model an equilibrium value h'^*_{INF} is a solution of the quadratic Eq. (22) (with all variables primed) and the solutions are given by the primed versions of Eqs. (23) and (24) with the results of Fig. 2 carrying over to the simplified model with primes added to R_0 and g_r. As in Theorem 1 the origin is stable if $R'_0 < 1$ and unstable if $R'_0 > 1$. The conjectures of Theorem 1 are true for the simplified model, namely:

(i) In region B the smallest positive solution $[(h'^{*(1)}_{INF}, v'^{*(1)}_{INF})]$ is unstable and the largest $[(h'^{*(2)}_{INF}, v'^{*(1)}_{INF})]$ is stable.
(ii) In region C the positive equilibrium point $[(h'^{*(2)}_{INF}, v'^{*(1)}_{INF})]$ is stable.

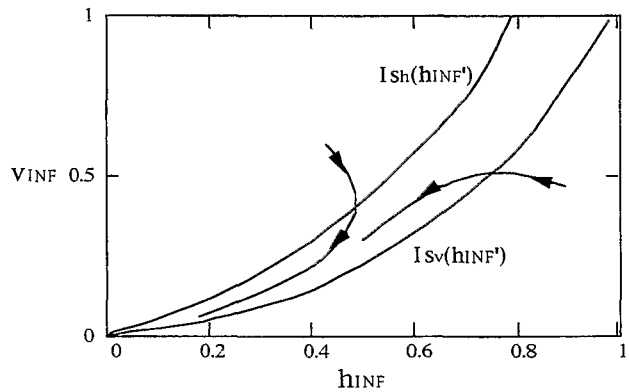
Proof. See Appendix 2.

Figure 3 depicts stylized examples of the possible scenarios for this simplified version of the model. The isoclines $Is_v(h'_{INF})$ and $Is_h(h'_{INF})$ (obtained by setting Eqs. (29) and (30) to zero) and examples of trajectories are represented. Depending on the values of (g'_r, R'_0) there is no positive equilibrium ($(g'_r, R'_0) \in A_1$ or A_2; Fig. 3(a)), two equilibria ($(g'_r, R'_0) \in B$; Fig. 3(b)) or one ($(g'_r, R'_0) \in C$; Fig. 3(c)).

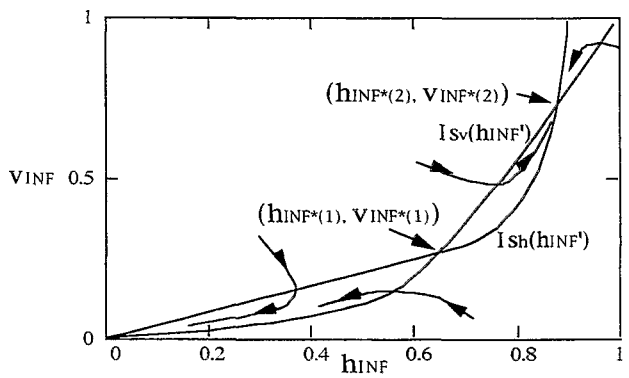
In the next section we will illustrate the models with parameter values estimated for the Niari focus in a savanna area in the Republic of Congo. Simulations will enable us to test the two models, compare them, and assess the impact of a control strategy that decreases the vector density V.

4. Simulations

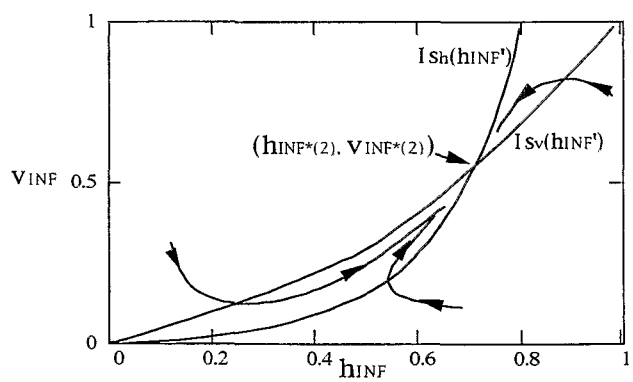
Discretized versions of both the original and the simplified models are used for the numerical simulations. The time-step is 1 (a three-day period equal to the average time between blood meals). This step is small enough for an equilibrium point to be stable for the discrete versions of the models whenever it is stable for the continuous models. (At least when the infection prevalence is not too high; in some cases when there is an equilibrium value h'^*_{INF} close to 1, the discretized version of the model can yield negative values and a smaller step would have to be taken — or other numerical schemes would have to be used. However we will limit ourselves to biologically realistic cases in which h'^*_{INF} is well under 1, say under 0.8, in which case the discretized version with a step of 1 can be used.)



(a) 0 is only stable equilibrium (Regions A1, A2)



(b) First positive equilibrium unstable; second stable (Region B)



(c) One stable positive equilibrium (Region C)

Fig. 3. Possible stability patterns of simplified model with isoclines.

In what follows the parameters g'_{in}, g'_a, g'_r, k'_{in} and k'_a of the simplified model will be taken equal to their unprimed counterparts of Eqs. (17) and (19). Both models will then be asymptotically equivalent in the neighborhood of a stable equilibrium point.

We will illustrate and compare the models with data estimated from the Niari focus which is in a savanna region of the Republic of Congo. One of the authors studied in this focus the effect on the epidemic of a reduction of the vector population (i.e., a decrease in V) [13,14].

The parameter values are chosen as follows:

(a) The mortality rates m_h and m_v were taken equal to 1.644×10^{-4} and $1/15$ which correspond to life expectancies of 50 years for humans [5] and 1.5 months for flies. This latter figure is an average value for a life expectancy that is somewhere between one and two months, depending on climatic conditions [11].

(b) We followed Rogers [27,29] in assuming that in the absence of the risk of mortality the average incubation periods are 25 days for vectors and 12 days for humans which translates into rates $q_v = 1/(25/3) = 0.12$ and $q_h = 1/(12/4) = 0.25$. The average sojourn time of a fly in the incubating compartment is then $1/(0.12 + 1/15)$ three-day periods which is about 16 days.

(c) We also assume with Rogers that $\tau_3 = 0.62$, which is just an order of magnitude for a parameter that is difficult to estimate. For τ_2 we choose 0.1, which is an average value in a range from 0.05 to 0.14 found for various species among the *palpalis* group of tsetse flies [1,20]. There is also considerable uncertainty concerning τ_1 which is known to be roughly in the range 0.05 to 0.25 [12,24]. In a savanna region there is no or little pig-rearing or game so we assume the highest value of 0.25 for τ_1.

(d) The parameter r_1 depends on the virulence of the parasite since its inverse is the average sojourn time in the first stage. This time, which is between a few months and several years, will be set at four months, which is a realistic value compatible with the observed virulence of the epidemic in Niari [9]. Thus $r_1 = 1/40 = 0.025$. Also r_2 will be taken equal to $1/80$, meaning an eight-month long removal period. This value is chosen to illustrate the widest possible range of behaviors of the system. The implications of a shorter removal time will also be discussed.

(e) The human population H will be taken equal to 300, which is a typical population of a village in the area considered. Finally the vector density V is usually a few thousand. To illustrate the uncertainties concerning V as well as the impact of a control strategy that can lower V, we will consider three possible values of V: 2,500, 3,000, and 3,500. With all other parameters fixed, these three values of V will define, in that order, three scenarios S_1, S_2, and S_3.

With these parameter values the quantity g_r (the proportion removed (see Eq. (17)) at or close to an equilibrium) is independent of V and is equal to 0.642.

The values of R_0 corresponding to the three scenarios are 0.824 (when $V = 2,500$); 0.989 ($V = 3,000$) and 1.154 ($V = 3,500$).

The three values of (g_r, R_0) are represented in Fig. 2 (noted S_1, S_2, and S_3) and show the three patterns that can be expected. For scenario S_1 (in A_1) the origin will be the only equilibrium point and it will be stable. For scenario S_2 (in B) the origin and another positive equilibrium point $(h^{*(2)}_{INF}, v^{*(2)}_{INF})$ will be stable (with $(h^{*(1)}_{INF}, v^{*(1)}_{INF})$ unstable). For S_3 there will be one positive equilibrium point $(h^{*(2)}_{INF}, v^{*(2)}_{INF})$. The values are given below in Table 1.

Table 1. Values of equilibria for the three illustrative scenarios S_1, S_2, and S_3.

V	R_0	$(h^{*(1)}_{INF}, v^{*(1)}_{INF})$	$(h^{*(2)}_{INF}, v^{*(2)}_{INF})$
2,500 (S_1)	0.824		
3,000 (S_2)	0.989	$(0.038, 3.207 \times 10^{-4})$	(0.677, 0.010)
3,500 (S_3)	1.154		(0.789, 0.013)

With an arbitrary initial point that is the same for both models, the trajectories of $(h_{INF}(t), v_{INF}(t))$ (obtained for the original model by summing infected populations; see Eq. (15)) and of $(h'_{INF}(t), v'_{INF}(t))$ for the simplified model, are depicted in Fig. 4 for the three scenarios. (The isoclines for the simplified model are also depicted.)

Figure 4(a) illustrates the convergence to extinction for both models in scenario S_1. (For the simplified model this figure corresponds to the stylization of Fig. 3(a)). The behavior is similar for both models although the prevalence of human infections increases more for the original model before the system goes to extinction.

The fact that extinction may be preceded by a transient increase in human infection (in parallel with a decrease in vector infection) may seem counter-intuitive. However such a phenomenon is caused by an initial surplus of infected vectors which causes a temporary increase in the human infected population even though extinction will eventually occur.

If the initial populations are between the two isoclines the convergence to extinction is monotone in both variables. This result is exact for the simplified model and holds as a rough approximation for the original model in a neighborhood of a stable equilibrium point. Indeed, Fig. 4(a) shows that $h_{INF}(t)$ stops increasing just when the trajectory crosses the $Is_h(h'_{INF})$ isocline, which shows that in this case the isocline provides accurate information on the original model which would otherwise be an intractable five-variable system not amenable to a graphic representation.

In Fig. 4(b) (scenario S_2 which corresponds to the stylization of Fig. 3(b)) there are two stable equilibria (the origin and $(h^{*(2)}_{INF}, v^{*(2)}_{INF})$ with $(h^{*(1)}_{INF}, v^{*(1)}_{INF})$ unstable). With the same initial populations as above, both trajectories converge with somewhat different paths to $(h^{*(2)}_{INF}, v^{*(2)}_{INF})$ even though R_0 is less than 1. (We recall that $R_0 < 1$ insures extinction only for an initial population close to the origin.) We also note that in this case $v_{INF}(t)$ stopped decreasing well before crossing

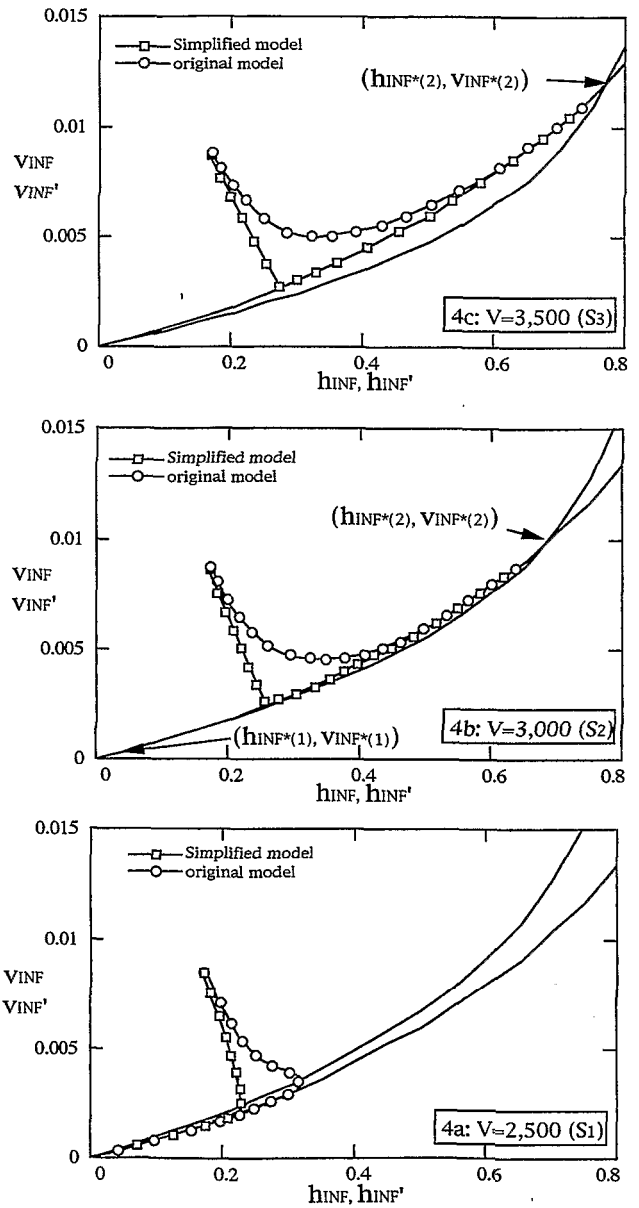


Fig. 4. Trajectories for both models under scenarios S_1, S_2 and S_3.

the $Is_v(h'_{INF})$ isocline even though both trajectories are generally similar. In this case both models converged to the same equilibrium point, but in other simulations not reported here one trajectory could converge to extinction and the other to $(h^{*(2)}_{INF}, v^{*(2)}_{INF})$. Thus both models can have dramatically different trajectories.

In Fig. 4(b), initial populations close to the origin converge to extinction, which shows how in this case different initial populations can drive the system to two possibly quite different equilibria. Different behaviors for different initial populations seem plausible and make biological sense. In the present example, the critical factor is the compartment of removed individuals not at risk of being bitten. Indeed, the removal of individuals from the risk of being bitten can have two opposite effects. On the one hand it decreases the number of persons a fly can bite, thus increasing the efficiency of transmission. On the other hand, if infected individuals are removed fast enough, then there are fewer infected individuals who can spread the disease. It is for these reasons that an initial population with a relatively large infected vector population can drive the system to a high infection prevalence by a rapid spread of the parasite that depletes the healthy population. With a smaller initial infected population of vectors, infected individuals can be removed fast enough to drive the epidemic to extinction.

In any event, the possible dependency of the equilibrium level on the initial population is biologically significant. Further studies will be needed, but these preliminary simulations suggest that initial populations as well as biological parameters could be used for intervention.

Finally in Fig. 4(c) (corresponding to the stylization of Fig. 3(c)) there is convergence for both models to the positive equilibrium $(h_{INF}^{*(2)},\ v_{INF}^{*(2)})$ regardless of the initial population.

A somewhat long sojourn time of eight months in the removed compartment was chosen to illustrate the possibility of the intriguing scenario with two stable points which can occur only for g_r larger than 0.5 (see Fig. 2). If the average time in the removed compartment is reduced to four or even two months (with aggressive forms of treatment, or perhaps a high induced mortality) the corresponding values of g_r drop to 0.476 and 0.312, respectively. R_0 does not change so that the three points S_1, S_2, and S_3 move horizontally to the left half of Fig. 2. When V decreases the system goes directly from one positive stable equilibrium (region C) to only the origin being stable (region A_2 then A_1).

In the Niari focus a drop of fifty percent in the vector density was obtained in a few weeks and the epidemic was brought to near extinction [13]. Given the numerous uncertainties in the estimates of R_0 and g_r for the Niari focus we would not claim to have truly validated these field results with our model. However, with plausible parameter values the model's conclusions are in general agreement with the observed extinction following a fifty percent drop in V. Indeed, Fig. 4 shows that a drop from say 5,000 to 2,500 will indeed bring about extinction, which suggests that the model is at least a plausible approximation to a complicated biological system.

5. Conclusion

In this paper we have described two models for the spread of sleeping sickness in Central Africa. The original model has five variables, and although we were able to study the existence of its equilibrium points, we were not able to study analytically the stability of equilibrium points other than the origin. Also, a dynamic system of five variables is difficult to represent graphically.

With the right parameter values, the simplified version of the model has the same equilibrium points; it is asymptotically equivalent to the original model close to an equilibrium point; and the stability of all these points can be studied analytically.

From a modeling point of view it is of interest to assess what was lost and what was gained with the simplified model. The main gain is the tractability of a simpler model that has the same features as the original one. In particular, the positive equilibrium points that were unmanageable in the original model became amenable at least to a local stability analysis. The cost one has to pay is a loss in realism caused by the constant infective structure hypothesis.

The models have enabled us to identify two important "summary parameters" that determine the equilibrium points: g_r, the proportion removed at an equilibrium and R_0, the basic reproduction rate. If R_0 is less than 1 then the origin is stable but there may also be a positive stable equilibrium if g_r is larger than 0.5 (region B). In this case the system will converge either to this positive equilibrium or to extinction, depending on the initial population. Indeed, if in such a situation the infected populations can be reduced (through treatment for humans and vector control for flies) then this one-time intervention can result in extinction, even if all epidemiological parameters remain at their pre-intervention values. Such scenarios need to be further explored, and the models proposed here will be useful tools for these and other investigations.

Acknowledgements

The authors wish to thank the two anonymous referees whose comments greatly improved this paper.

Appendix 1. Proof of Theorem 1

The discriminant of the quadratic Eq. (22) is $R_0(R_0 - 4g_r + 4g_r^2)$. The product of the roots is $(1 - R_0)/g_r^2$ and their sum is $(2g_r - R_0)/g_r^2$. Therefore both roots are complex if and only if $R_0 < 4g_r(1 - g_r)$ (region A_1). If $1 > R_0 > 4g_r(1 - g_r)$ and $g_r < 0.5$ the product is positive and the sum negative so both roots are negative (region A_2). If $1 > R_0 > 4g_r(1 - g_r)$ and $g_r > 0.5$ the product and the sum of the roots are positive so both roots are positive (region B). If $R_0 > 1$ the product and the sum of the roots are negative so there is one root of each sign (region C). This completes the proof concerning the existence of equilibrium points.

To study the stability of the system we consider the Jacobian matrix at an equilibrium point $(v_{in}^*, v_a^*, h_{in}^*, h_a^*, h_r^*)$:

$$J(v_{in}^*, v_a^*, h_{in}^*, h_a^*, h_r^*) =$$

$$\begin{pmatrix} -q_v - m_v & 0 & 0 & \frac{\tau_1 \tau_2 m_v}{1-h_r^*} & \frac{\tau_1 \tau_2 m_v h_a^*}{(1-h_r^*)^2} \\ q_v & -m_v & 0 & 0 & 0 \\ 0 & \frac{V\tau_1(-1+h_r^*+h_a^*+h_{in}^*)}{(-1+h_r^*)H} & \frac{-\tau_1 v_a^* V}{(1-h_r^*)H} - m_h - q_h & \frac{-\tau_1 v_a^* V}{(1-h_r^*)H} & \frac{-\tau_1 v_a^* V(h_a^*+h_{in}^*)}{(-1+h_r^*)^2 H} \\ 0 & 0 & q_h & -r_1 - m_h & 0 \\ 0 & 0 & 0 & r_1 & -m_h - r_2 \end{pmatrix} \tag{A.1}$$

The equilibrium point is stable if the real parts of the eigenvalues of this matrix are negative. The eigenvalues are the solutions of a polynomial equation of order five that is intractable, except at the origin. Indeed, setting $(v_{in}^*, v_a^*, h_{in}^*, h_a^*, h_r^*)$ equal to 0 in (A.1) yields a simpler matrix whose characteristic polynomial $P(x)$ is

$$\begin{aligned} P(x) = [&-\tau_1^2 \tau_2 m_v q_v V q_h / H + (r_1 + m_h + x)(q_v + m_v + x)(m_v + x) \\ &\times (m_h + q_h + x)][-m_h - r_2 - x]. \end{aligned} \tag{A.2}$$

One root is $x = -m_h - r_2$ which is always negative, and the four other roots are the solutions of the polynomial equation of order four:

$$Q(x) = -\tau_1^2 \tau_2 m_v q_v V q_h / H + (r_1 + m_h + x)(q_v + m_v + x)(m_v + x)(m_h + q_h + x) = 0. \tag{A.3}$$

We will now prove the desired result by showing that if $R_0 > 1$ there is a positive root and if $R_0 < 1$ no root can have a nonnegative real part.

Equation (A.3) is equivalent to

$$R_0 = \left(\frac{r_1 + m_h + x}{r_1 + m_h}\right)\left(\frac{q_v + m_v + x}{q_v + m_v}\right)\left(\frac{m_v + x}{m_v}\right)\left(\frac{m_h + q_h + x}{m_h + q_h}\right). \tag{A.4}$$

The right-hand side of (A.4) is equal to 1 for $x = 0$ and increases monotonically to infinity for $x \to \infty$. Therefore, if $R_0 > 1$ there is necessarily a positive solution and 0 is unstable. If $R_0 < 1$ then there cannot be a positive solution of the equation (since for $x > 0$ the right-hand side of (A.4) is larger than 1).

We now need to prove that for $R_0 < 1$ there is no complex root x with nonnegative real part. If such a root existed its argument θ would satisfy $0 < \theta \leq \pi/2$ or $-\pi/2 \leq \theta < 0$. We will show that no such root can exist with $0 < \theta \leq \pi/2$ which will complete the proof since complex roots come in conjugate pairs. If $0 < \theta \leq \pi/2$ then regardless of the modulus of x each one of the four terms on the right-hand side of (A.4) is a complex number with a positive argument strictly less than $\pi/2$. The argument of the number on the right-hand side of (A.4) is therefore positive and strictly less than 2π and therefore the r.h.s of (A.4) cannot be equal to the

positive number R_0. We note that this is in fact true for any value of R_0, and not only for $R_0 < 1$. We have therefore shown that for any R_0 there cannot be a complex root with nonnegative real part. (Although we showed earlier that there is a *positive* root for $R_0 > 1$.)

Appendix 2. Proof of Theorem 2

Proof. The derivation of the quadratic equation and the analysis of Fig. 2 is similar to that of Theorem 1. In particular (0,0) is an equilibrium point and a non-zero equilibrium h'^*_{INF} is a positive solution, when it exists, of the quadratic equation

$$hg_r'^2 - (2g_r' - B_0')h + 1 - R_0' = 0\,. \tag{B.1}$$

The equilibrium value v'^*_{INF} is obtained by setting Eq. (29) equal to 0. The stability analysis relies on the Jacobian matrix of the system at an equilibrium (h'^*_{INF}, v'^*_{INF}) which is

$$J(h'^*_{INF}, v'^*_{INF}) = \begin{pmatrix} \dfrac{\tau_1^2\tau_3 v'^*_{INF} k_a' V(g_r'-1)}{H(g_r' h'^*_{INF}-1)^2} - m_h - g_r' r_2 & \dfrac{\tau_1\tau_3 k_a' V(1-h'^*_{INF})}{H(1-g_r'\cdot h'^*_{INF})} \\ \dfrac{m_v\tau_1\tau_2 g_a'}{(g_r' h'^*_{INF}-1)^2} & -m_v \end{pmatrix}. \tag{B.2}$$

Given that the trace of this matrix is negative, the sum of the two eigenvalues is also negative. The real parts of the eigenvalues will then be negative if and only if the determinant of this matrix is positive (since the determinant is equal to the product of the eigenvalues).

The results concerning the stability of the origin follow directly from the fact that

$$\mathrm{Det}[J(0,0)] = (1-R_0')m_v(m_h + g_r' r_2)\,. \tag{B.3}$$

The origin is therefore stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Long but elementary calculations show that at an equilibrium point (h'^*_{INF}, v'^*_{INF}) other than the origin we have

$$\mathrm{Det}[J(h'^*_{INF}, v'^*_{INF})] = \frac{h'^*_{INF} m_v(m_h + g_r' r_2) H(g_r' h'^*_{INF} - 2g_r' + 1)}{(1-h_{INF})(1-g_r' h'^*_{INF})H}\,. \tag{B.4}$$

The sign of this determinant is therefore the same as that of $(g_r' h'^*_{INF} - 2g_r' + 1)$. For h'^*_{INF} equal to either one of the two roots $h'^{*(k)}_{INF} (k = 1, 2)$ we have

$$g_r' h'^{*(k)}_{INF} - 2g_r' + 1 = -0.5\,\frac{R_0' + 4g_r'(g_r'-1) - (-1)^k\sqrt{R_0'}\sqrt{R_0' + 4g_r'(g_r'-1)}}{g_r'}\,. \tag{B.5}$$

When (g_r', R_0') is in B or C (Fig. 2) then $h'^{*(2)}_{INF} > 0$ and for $k = 2$ the right-hand side of Eq. (B.5) is positive. When (g_r', R_0') is in B, then $h'^{*(1)}_{INF}$ is also positive and for $k = 1$ the right-hand side is negative which completes the proof.

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