

# African trypanosomiasis or “Sleeping sickness”

A bio-mathematical study of the disease

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## A bio-mathematical study of the disease

*African trypanosomiasis, commonly known as sleeping sickness, is one of the most infectious diseases in the African continent. It is a parasitic disease that can lead to an acute or a chronic infection. In the following paper, we study sleeping sickness from both biological and mathematical points of view, and we try to set up a model for the disease from the biological information we have.*

### History of the disease

African trypanosomiasis is caused by two different species of trypanosomes, namely *Trypanosoma brucei gambiense* (Tbg) in West and Central Africa, and *Trypanosoma brucei rhodesiense* (Tbr) in East Africa, and is transmitted by the tsetse fly. It is not a recently known disease, since it has been present for thousands of years before. There have been three particularly severe epidemics during the twentieth century. The first was from 1896 until 1906 in Uganda and the Congo basin, the second during the 1920s, and the third began in the 1970s and continues until the present time. In fact, recently in 2008 there was an epidemic in Uganda. Intensive systematic screening by mobile teams, of many millions of people per year at risk, halted the epidemic of the 1920s. The illness was practically eliminated by 1960. Such active population screening was not continued, at least partly because the disease had nearly disappeared from Africa. Not surprisingly, with the breakdown of the control system, the disease has re-emerged as a major health problem in recent years.

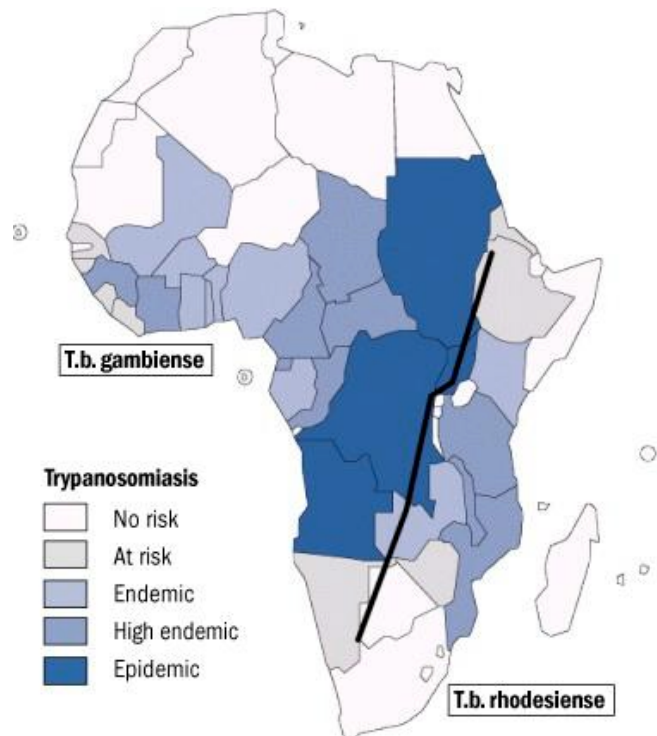
### Geographic distribution

Sleeping sickness is found uniquely in sub-Saharan Africa, it is endemic in some regions there, mainly in the regions where the tsetse fly is constantly present.

Almost 45,000 cases of African sleeping sickness were reported to the World Health Organization (WHO) in 1999, but the WHO believes the real number of cases is between 300,000 and 500,000 cases. In specific villages of many provinces of Angola, the Democratic Republic of Congo and southern Sudan, the prevalence of the disease is 20% to 50%. Sleeping sickness has become the second greatest cause of death, after HIV/AIDS, in those areas.

An important feature of African trypanosomiasis is its focal nature. It tends to occur in circumscribed zones.

Observed prevalence rates vary greatly from one geographical area to another, and even between one village and another within the same area. Thus, it is important to understand the ecology and resulting transmission patterns in each locality.

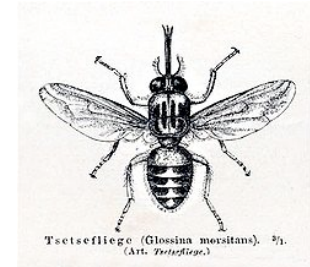


## Transmission and symptoms

African trypanomiasis is transmitted mainly from bites of infected tsetse flies, living in areas surrounding human habitats such as cultivated land, and near small rivers or pools of water, frequented by people. Thus, there is close contact between people and tsetse flies as people go about their daily activities. However, only infected tsetse flies cause infection. Transmission is also possible through contamination with infected blood (in laboratories, blood transfusion) or from mother to child through the placenta, but this latest case usually leads to abortion or prenatal death.

The bite of tsetse fly can be very painful and the probability of getting infected increases as the number of the bites increase. Gambiense sleeping sickness is a chronic disease with a long latency period and people can be infective for many

years without knowing. Rhodesiense sleeping sickness is much more virulent than gambiense and infected people usually die within a matter of months. Both types of sleeping sickness are fatal if left untreated.



Symptoms include fever, rash, swelling around the eyes and hands, severe headaches, extreme fatigue, swollen lymph nodes, and aching muscles and joints. If untreated in this first stage, the disease slowly overcomes the defenses of the infected person, and symptoms spread to include anemia, endocrine, cardiac, and kidney diseases and disorders. The disease then enters a neurological phase when the parasite passes through the blood-brain barrier. The symptoms of the second phase give the disease its name; besides confusion and reduced coordination, the sleep cycle is disturbed with bouts of fatigue punctuated with manic periods progressing to daytime slumber and nighttime insomnia. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma and death. Damage caused in the neurological phase can be irreversible.

### **Treatments and their efficacy**

Medications are available for the treatment of African trypanosomiasis. Treatment should begin as soon as possible following exposure to arrest the progression of the disease. However, diagnosis of African trypanosomiasis can be challenging, particularly for *Trypanosoma brucei gambiense* which has a long latency period, making early treatment difficult. The disease is diagnosed through blood and spinal fluid tests.

If the disease is diagnosed early, the chances of cure are high. The type of treatment depends on the phase of the disease: initial or neurological. Success in the latter phase depends on having a drug that can cross the blood-brain barrier to reach the parasite. Most drugs are old, difficult to administer in poor conditions and by no means always successful. Four drugs have been used until now. Unfortunately, however, those medications effective against the sleeping sickness all have significant potential side effects for the patient. Suramin, eflornithine,

pentamidine, and several drugs which contain arsenic, a chemical which in higher doses is highly poisonous to humans, are all effective anti-trypanosomal agents. Each of these drugs, however, requires careful monitoring to ensure that the drugs themselves do not cause serious complications such as fatal allergic reaction, kidney or liver damage, or inflammation of the brain.

## The mathematical model

The mathematical model for African trypanomiasis is deduced from the transmission methods and includes also population dynamics. It is defined as follows:

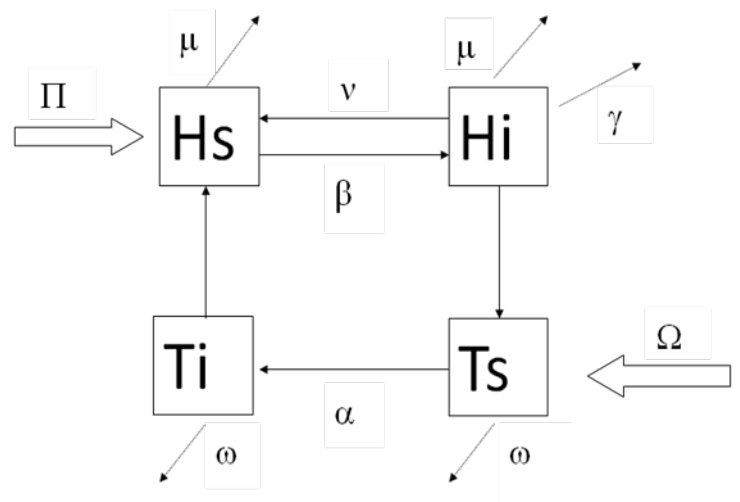
- Susceptible people are born at rate  $\pi$
- Susceptible tsetse flies are born at rate  $\Omega$
- The death rate for humans is  $\mu$
- The death rate for tsetse flies is  $\omega$
- The disease specific death rate for humans is  $\gamma$
- The recovery rate is  $\nu$
- Susceptible people become infected from a tsetse bite, or from infected blood contact. Infection rate is  $\beta$
- A tsetse fly becomes infected when taking an infected blood meal from an infected human. Infection rate is  $\alpha$

$$\frac{dH_s}{dt} = \pi - \beta H_s T_i - \mu H_s + \nu H_i$$

$$\frac{dH_i}{dt} = \beta H_s T_i - (\mu + \gamma + \nu) H_i$$

$$\frac{dT_s}{dt} = \Omega - \alpha H_i T_s - \omega T_s$$

$$\frac{dT_i}{dt} = \alpha H_i T_s - \omega T_i$$



H: Humans      T: Tsetse flies

i: Infected      s: Susceptible

## Mathematical analysis: equilibriums and their stability

a) Equilibrium occur when the derivates = 0. For this model, we have two equilibrium points:

- Disease free equilibrium DFE=  $(\frac{\pi}{\mu}, 0, \frac{\Omega}{\omega}, 0)$
- Endemic equilibrium=  $(\bar{H}_s, \bar{H}_i, \bar{T}_s, \bar{T}_i)$

$$= (\frac{\pi}{\mu} - \frac{\mu+\gamma}{\mu} H_i, H_i, \frac{\omega T_s}{\alpha H_i}, \frac{\pi - \mu H_s + \nu H_i}{\beta H_s})$$

b) To determine the stability of the DFE, we use the Jacobian method, with the corresponding matrix:

$$J = \begin{bmatrix} -\beta T_i - \mu & \nu & 0 & -\beta H_s \\ \beta T_i & -(\mu + \gamma + \nu) & 0 & \beta H_s \\ 0 & -\alpha T_s & -\alpha H_i - \omega & 0 \\ 0 & \alpha T_s & \alpha H_i & -\omega \end{bmatrix}$$

$$J_{DFE} = \begin{bmatrix} -\mu & \nu & 0 & -\beta H_s \\ 0 & -(\mu + \gamma + \nu) & 0 & \beta H_s \\ 0 & -\alpha T_s & -\omega & 0 \\ 0 & \alpha T_s & 0 & -\omega \end{bmatrix}$$

$$\text{Det}(J_{DFE} - \lambda I) = (-\mu - \lambda)(-\omega - \lambda)[\lambda^2 + (\mu + \gamma + \nu + \omega)\lambda + (\mu + \gamma + \nu)\omega - \frac{\beta\pi\alpha\Omega}{\mu\omega}]$$

Since the first two eigenvalues  $-\mu$  and  $-\omega$  are negative, the stability is determined by the expression in brackets. This expression is of the form  $\lambda^2 + b\lambda + c$  with  $b > 0$ . So the constant term  $c$  is the factor that determines the stability of the DFE as follows:

- DFE is stable if  $c > 0$ , i.e.  $\frac{\beta\pi\alpha\Omega}{\mu\omega^2(\mu + \gamma + \nu)} < 1$
- DFE is unstable if  $c < 0$ , i.e.  $\frac{\beta\pi\alpha\Omega}{\mu\omega^2(\mu + \gamma + \nu)} > 1$

Hence we can define  $R_0 = \frac{\beta\pi\alpha\Omega}{\mu\omega^2(\mu + \gamma + \nu)}$  as the number of secondary

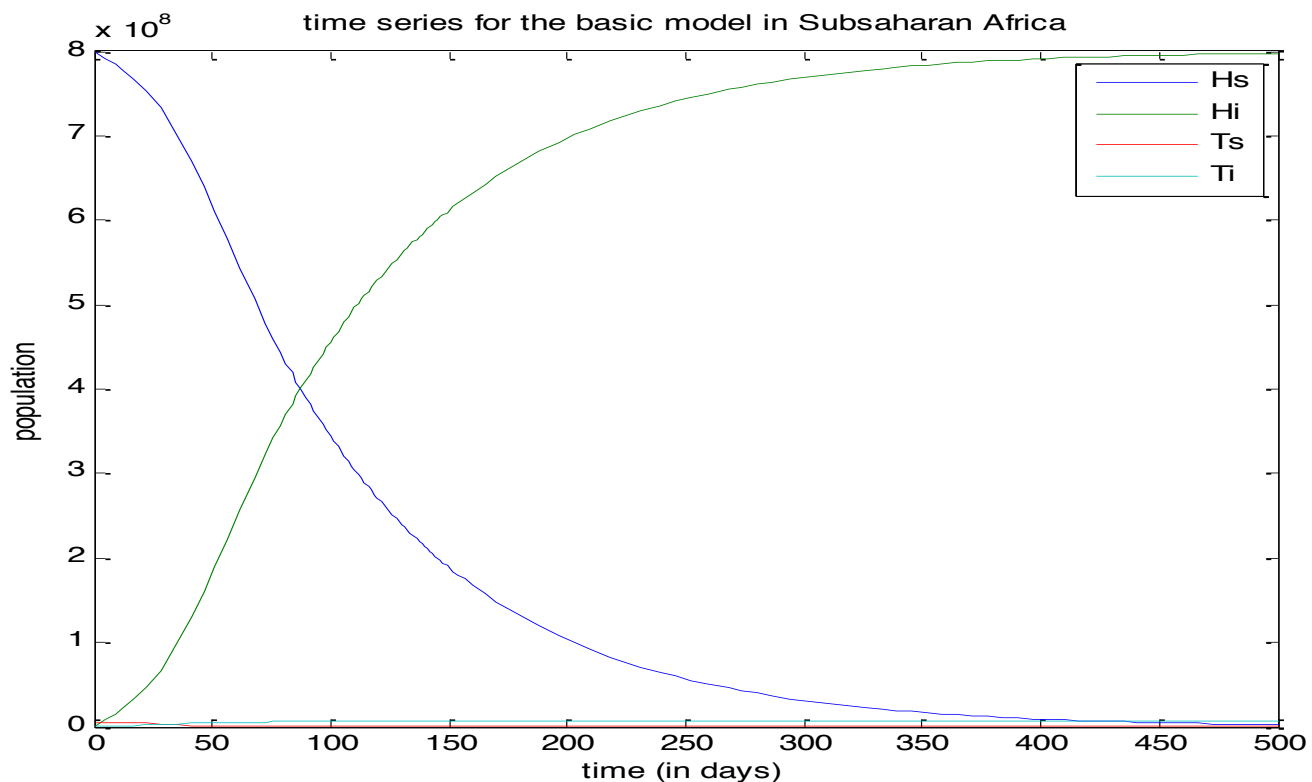
infections caused by an infected individual.

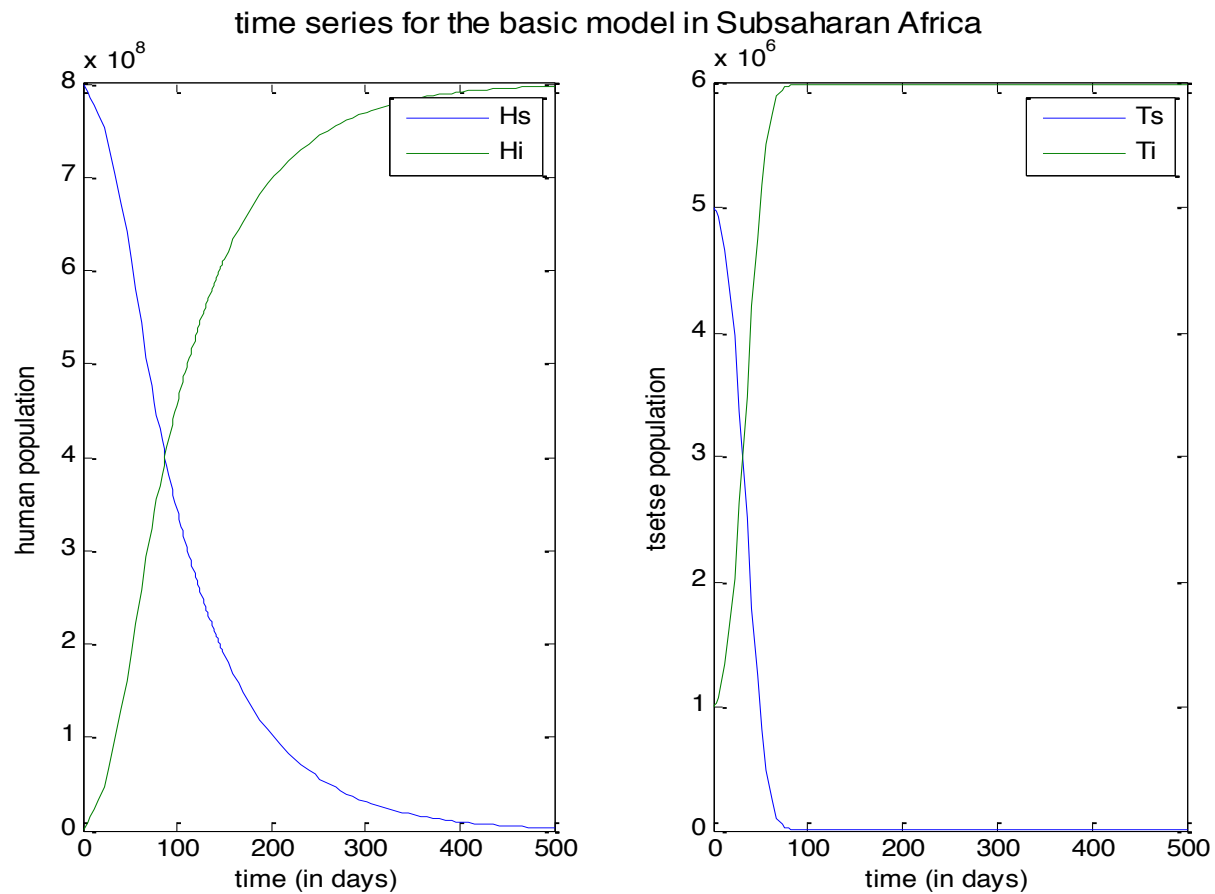
## Numerics for the model

In this section, we try to visualize the behaviour of sleeping sickness in the large zone of Subsaharan Africa in general, where 800 million people are in risk of getting infected, and half a million people are actually infected. So if we suppose a sudden outbreak of rodesiense trypanosomiasis occurred this region, what would happen?

The parameters used are resumed in the following table:

$\pi$	5 humans/day	5 people are born every day
$\mu$	$1/21900 \text{ day}^{-1}$	Average lifetime of 60 years
$\beta$	$0.002 \text{ tsetse}^{-1}.\text{day}^{-1}$	2% chance of getting infected from a tsetse bite
$\nu$	$1/7 \text{ day}^{-1}$	Average treatment duration of 7 days
$\gamma$	$1/21 \text{ days}^{-1}$	Disease specific death rate
$\Omega$	20 tsetse/day	20 tsetse are born everyday
$\omega$	$1/90 \text{ days}^{-1}$	Average lifetime of a tsetse fly is 3 months
$\alpha$	$0.0005 \text{ human}^{-1}.\text{day}^{-1}$	0.5% chance for a tsetse getting infected from a human





As we can see, the plots predict an endemic state of the disease in the Subsaharan African population after a certain time, and because of the virulence of this rodesiense type, and the increase in the infected tsetse population, everyone will become infected. Well this is an “apocalyptic” scenario somehow, and we can see that the need of an efficient treatment is urgent.



## Introducing a vaccine

There is no vaccine for the prevention of African trypanosomiasis. But in this paper, we try to investigate the impact of introducing a vaccine on the disease control. So We suppose there exists a vaccine that automatically takes, does not give permanent immunity but reduces the fatality of the disease symptoms i.e. reduce disease specific death rate (vaccine “success”) and may wane over time (probably in a short time period, 2 years approximately). The model gets more complicated, and we introduce new parameters:

- The proportion of the population vaccinated is  $p$
- The waning rate is  $\xi$
- The specific death rate for the infected vaccinated humans is  $\gamma'$  (clearly  $\gamma' < \gamma$ )

$$\frac{dH_{su}}{dt} = (1-p)\pi - \mu H_{su} - \beta H_{su} T_i + \nu H_{iu} + \xi H_{sv}$$

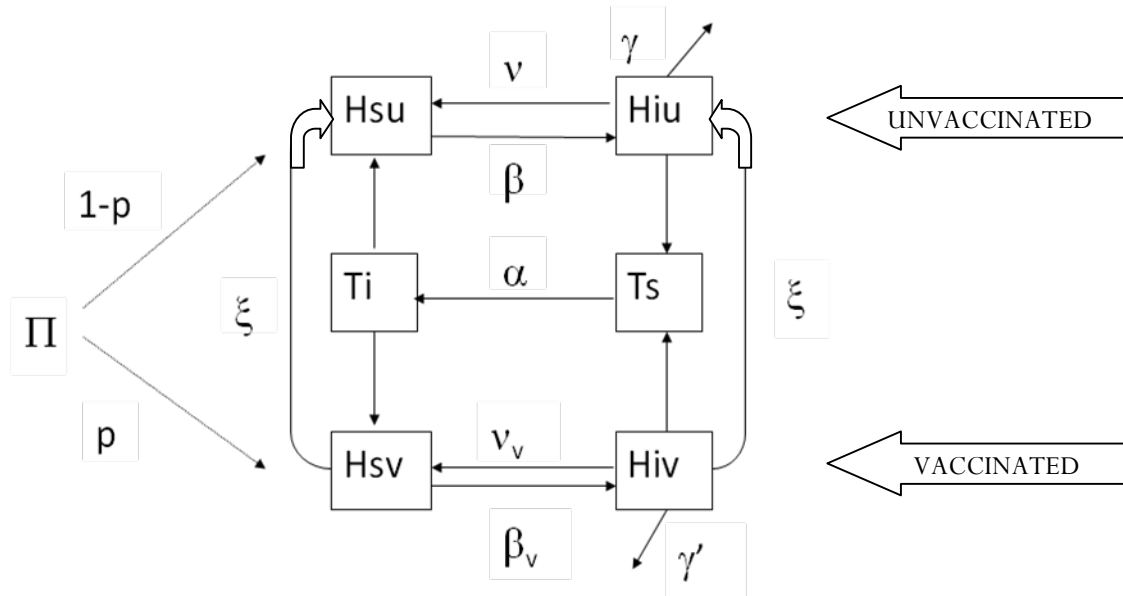
$$\frac{dH_{iu}}{dt} = \beta H_{su} T_i - (\mu + \gamma + \nu) H_{iu} + \xi H_{iv}$$

$$\frac{dH_{sv}}{dt} = p\pi - \mu H_{sv} - \beta_v T_i H_{sv} - \xi H_{sv} + \nu_v H_{iv}$$

$$\frac{dH_{iv}}{dt} = \beta_v T_i H_{sv} - (\mu + \nu_v + \gamma') H_{iv} - \xi H_{iv}$$

$$\frac{dT_s}{dt} = \Omega - \alpha H_{iu} T_s - \alpha H_{iv} T_s - \omega T_s$$

$$\frac{dT_i}{dt} = \alpha H_{iu} T_s + \alpha H_{iv} T_s - \omega T_i$$



## Mathematical analysis for the new model

The disease free equilibrium in this case is:

$$DFE = \left( \frac{\pi(\mu + \xi - p\pi)}{\mu(\mu + \xi)}, 0, \frac{p\pi}{\mu + \xi}, 0, \frac{\Omega}{\omega}, 0 \right)$$

Again we use the Jacobian method to determine the stability of the DFE:

J =

$$J_{DFE} = \begin{bmatrix} -\mu - \beta T_i & \nu & \xi & 0 & 0 & -\beta H_{su} \\ \beta T_i & -(\mu + \gamma + \nu) & 0 & \xi & 0 & \beta H_{su} \\ 0 & 0 & -\mu - \xi - \beta_v T_i & \nu_v & 0 & -\beta_v H_{sv} \\ 0 & 0 & \beta_v T_i & -(\mu + \nu_v + \gamma' + \xi) & 0 & \beta_v H_{sv} \\ 0 & -\alpha T_s & 0 & -\alpha T_s & -\alpha H_{iv} - \alpha H_{iu} - \omega & 0 \\ 0 & \alpha T_s & 0 & \alpha T_s & \alpha H_{iv} + \alpha H_{iu} - \omega & -\omega \end{bmatrix}$$

Det( $J_{DFE} - \lambda I$ ) =  $(-\mu - \lambda)(-\omega - \lambda)(-\mu - \xi - \lambda)\det(M)$  where

$$M = \begin{bmatrix} -(\mu + \gamma + \nu) & \xi & \beta H_{su} \\ 0 & -(\mu + \nu_v + \gamma' + \xi) & \beta_v H_{sv} \\ \alpha T_s & \alpha T_s & -\omega \end{bmatrix}$$

The eigenvalues  $-\mu$ ,  $-\omega$  and  $-\mu - \xi$  are all negative, so they don't affect the stability. So we can reduce the problem to solving  $\det(M) = 0$  which is of the form  $\lambda^3 + a\lambda^2 + b\lambda + c = 0$  with:

$$a = \omega + \gamma + \gamma' + \nu + \nu_v + \xi + 2\mu \quad (a > 0)$$

$$b = (\mu + \nu_v + \gamma' + \xi)(\omega + \mu + \gamma + \nu) + \omega(\mu + \gamma + \nu) - \alpha T_s \beta_v H_{sv} - \alpha T_s \beta H_{su}$$

$$c = (\mu + \gamma + \nu)[\omega(\mu + \nu_v + \gamma' + \xi) - \alpha T_s \beta_v H_{sv}] - \alpha \xi T_s \beta_v H_{sv}$$

$$- \alpha T_s \beta H_{su}(\mu + \nu_v + \gamma' + \xi)$$

We can show that  $b > 0$ :

- Analytically, it is not as simple as we wish because of the number of parameters we have in the model (13 parameters!)
- Numerically, it is easier if we use the same set of parameters used in the corresponding Matlab code

Therefore we can use the vanishing determinant condition:  $c = 0$

And by rearranging this equation, we have:

$$\left[ \frac{\alpha T_s \beta_v}{\omega(\mu + \nu_v + \gamma' + \xi)} + \frac{\alpha \xi T_s \beta_v}{\omega(\mu + \gamma + \nu)(\mu + \nu_v + \gamma' + \xi)} \right] H_{sv} + \frac{\alpha T_s \beta}{\omega(\mu + \gamma + \nu)} H_{su} = 1$$

-If there is no vaccination,  $H_{sv} = 0$ ,  $H_{su} = \pi/\mu$ ,  $T_s = \Omega/\omega$

$\Rightarrow R_0 = \frac{\beta \pi \alpha \Omega}{\mu \omega^2 (\mu + \gamma + \nu)}$  which is the same one from the previous section of the original model

-If the population is successfully vaccinated,  $H_{sv} = \pi/\mu$ ,  $H_{su} = 0$

$$\Rightarrow R_v = \left[ \frac{1}{\omega(\mu + \nu_v + \gamma' + \xi)} + \frac{\xi}{\omega(\mu + \gamma + \nu)(\mu + \nu_v + \gamma' + \xi)} \right] \frac{\alpha \beta_v \Omega \pi}{\omega \mu}$$

We then define the basic reproductive numbers  $R_0$  and  $R_v$ , and the population reproductive number  $R_p$ :

- $R_0$  is the number of secondary infections caused by an infected unvaccinated individual
- $R_v$  is the number of secondary infections caused by an infected vaccinated individual
- $R_p$  is the total number of secondary infections caused by a single individual;  $R_p = S R_v + (1-S) R_0$  with  $S$  the proportion successfully vaccinated

$$S = \frac{\text{number of infected}}{\text{total population}} = \frac{\overline{H_{sv}}}{\overline{H_{sv}} + \overline{H_{su}}} = \frac{p\mu}{\mu + \xi}$$

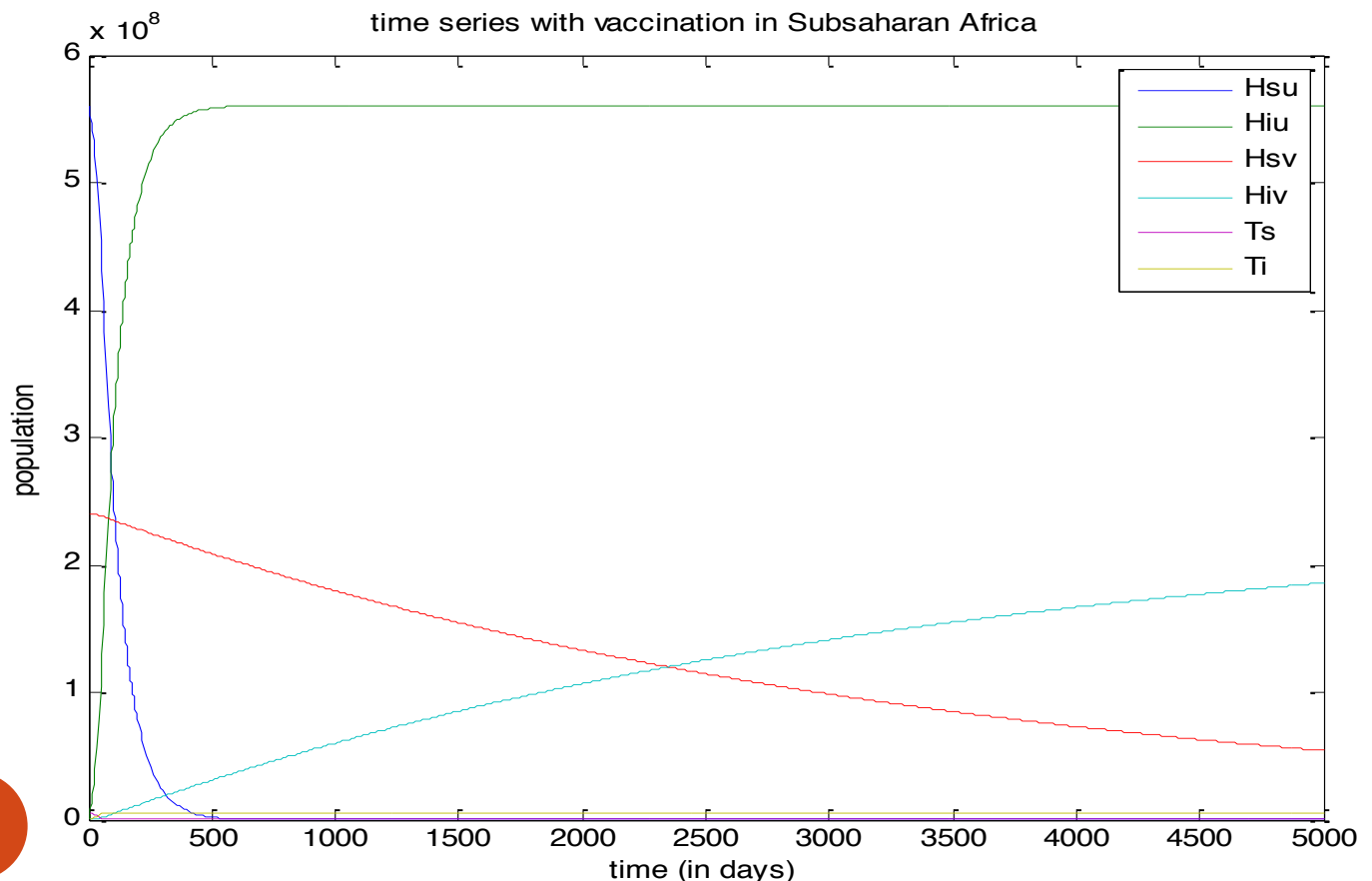
For such an imperfect vaccine and under the assumption that  $R_p = 1$ , we can determine the minimal vaccinating coverage level  $p_c$ , or the minimum proportion of people that should be vaccinated in order to stop the disease from spreading.

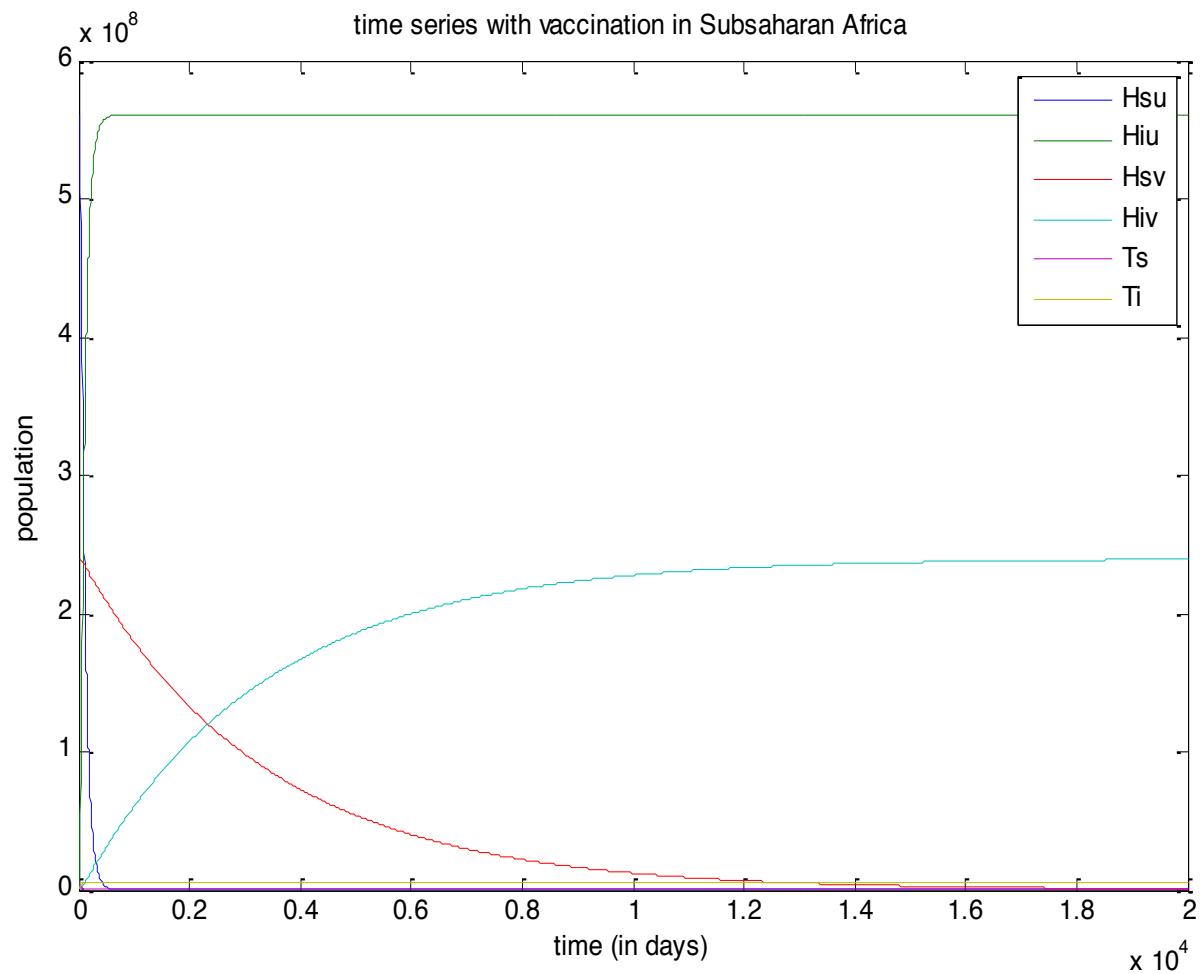
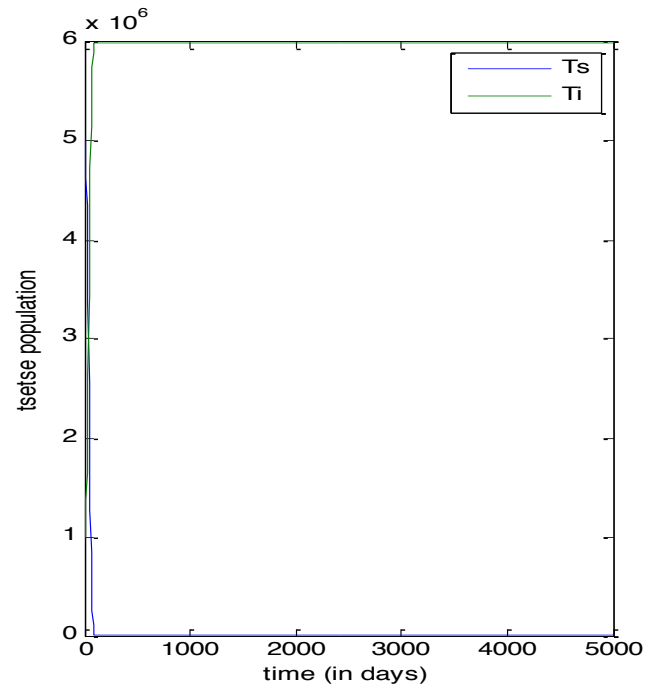
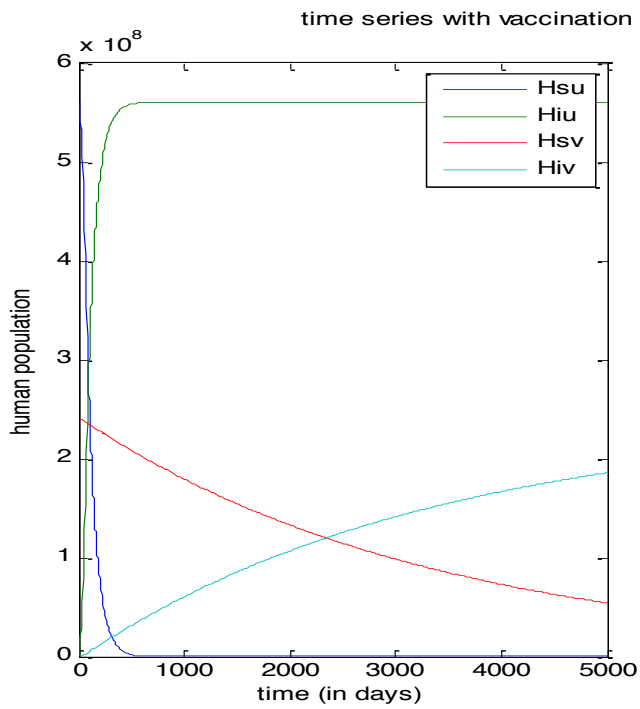
$$S = \frac{p_c \mu}{\mu + \xi} = \frac{1 - R_0}{R_v - R_0} \Rightarrow p_c = \frac{(\mu + \xi)(1 - R_0)}{\mu(R_v - R_0)}$$

### Numerics for the model with vaccination

We keep the same parameters as in the original model, and we introduce 5 new parameters:

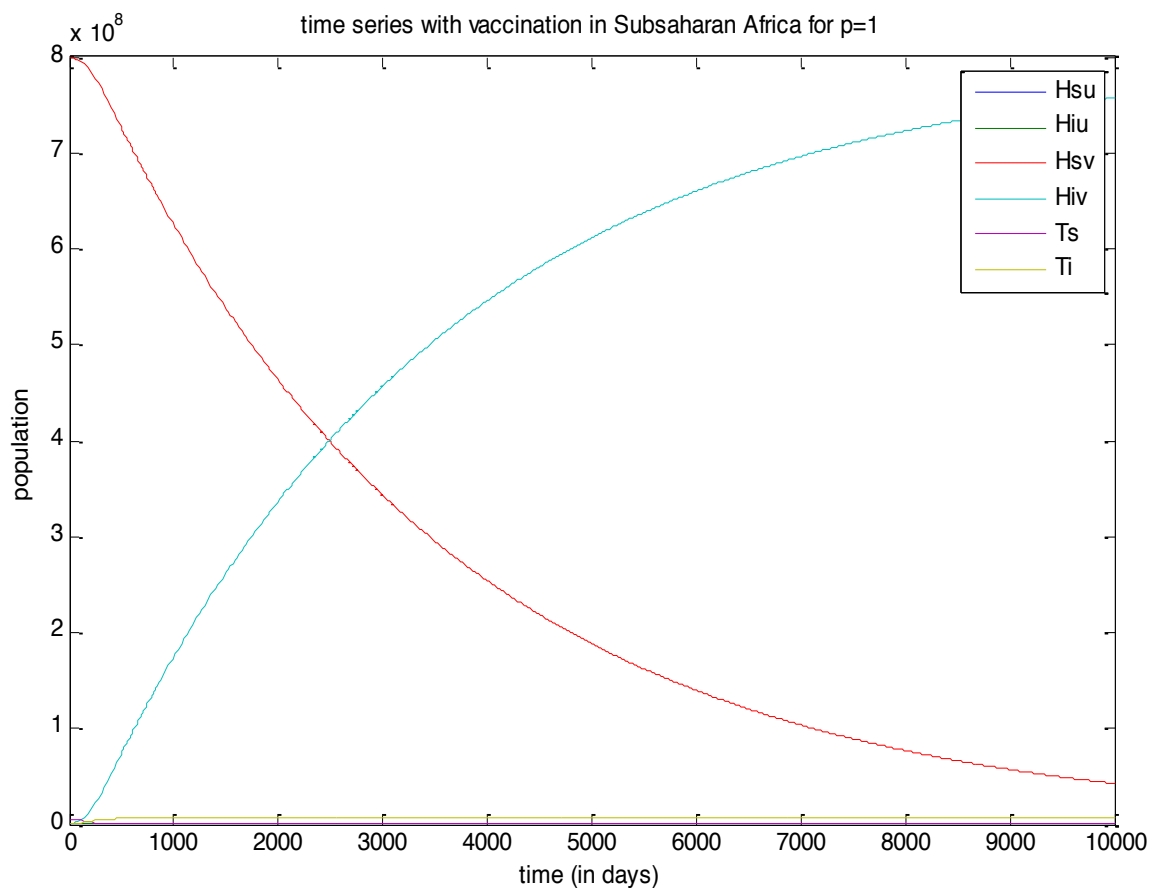
$\beta_v$	0.00005 tsetse <sup>-1</sup> .day <sup>-1</sup>	0.005% chance of getting infected from a tsetse bite
$\nu_v$	1/3 day <sup>-1</sup>	Average recovery period of 3 days
$\gamma'$	1/75 day <sup>-1</sup>	Disease specific death rate with vaccination
$p$	0.3	Proportion vaccinated of the population
$\xi$	1/730 day <sup>-1</sup>	Waning of the vaccine after 2 years





## Results

So what is the impact of vaccination? What we can say is that vaccination did not prevent the endemic, it only slowed it. And after a longer time, we can see that all vaccinated people become infected vaccinated people, so we have the same behaviour as the previous case without vaccination, but in a slower speed. Even if we manage to have a 100% coverage for the vaccine, i.e. if we could vaccinate all the population, the result would be the same. So it would always be a temporary solution and not a permanent one.



However, this prevention measure is still helpful, because even with a vaccine lifetime of 2 years only, we have approximately 5 years before the endemic gets worst, so there is enough time for urgent interventions, treatments and necessary health measures.

## **Conclusion and some recommendations**

A next aim in future researches would be to investigate the effect of a more efficient vaccine that ensures a longer immunity, and if such a perfect vaccine cannot be found in reality, what could happen if a “fast-waning” vaccine (similar to the assumptions in this paper, of a 2 years coverage) was administered several times in a lifetime. On the other hand, can a regular screening be more efficient than vaccination?

While efficient treatments for African trypanosomiasis are not available yet, precaution is strongly recommended. Some personal measures to reduce exposure to tsetse flies vary from wearing protective clothes, using screens or bed nets while sleeping, and checking the inside of the car for tsetse flies before getting in it. Surprisingly, insect repellent does not prevent tsetse bites. So, in case of a bite, if the person develops the disease` symptoms, treatment should start as soon as possible (while the infection is in the first stage), and is successful in most of the cases. Testing and diagnose are also recommended at all time, to prevent developing a chronic infection without knowing.

Eradicating African trypanosomiasis is an ecological issue as much as it is medical. It would be very interesting to pursue some researches concerning the best methods to control tsetse species or the optimal efficacy of using insecticides in the affected African regions.

It is urgent that systematic population screening in high-risk areas, together with appropriate treatment be re-established. The need for technical expertise for testing and treating patients, which is not available at peripheral health facilities, is necessary. Because of this, most cases are not detected, not treated, and therefore fatal. Availability of medications at affordable prices in the African continent would also be beneficial for patients. However, developing an adequate vaccine for sleeping sickness could be the best solution to reduce infections.

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