Modeling the control of trypanosoma brucei rhodesiense through mass chemoprophylaxis and insecticide—treated cattle.

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Outlines:

- Background
- Mathematical models of African Trypanosomiasis
- Discussion and conclusion
- Work in progress

I. Background:

- African trypanosomiasis is a vector born disease caused by a parasite that is transmitted by tsetse flies
- African trypanosomiasis affects both humans and animals.
  - Human African trypanosomiasis (HAT) is fatal if untreated.
  - The average number of cases of HAT recorded per year has ranged between ~38000 (1998) and ~7000 (2011).
  - Animal African trypanosomiasis (AAT) is fatal to some livestock species and has a significant impact on their productivity.
  - AAT kills more than 1 million cattle each year
- The annual economic loss due to combined impact of HAT and AAT has been estimated at $2-4.5 billion

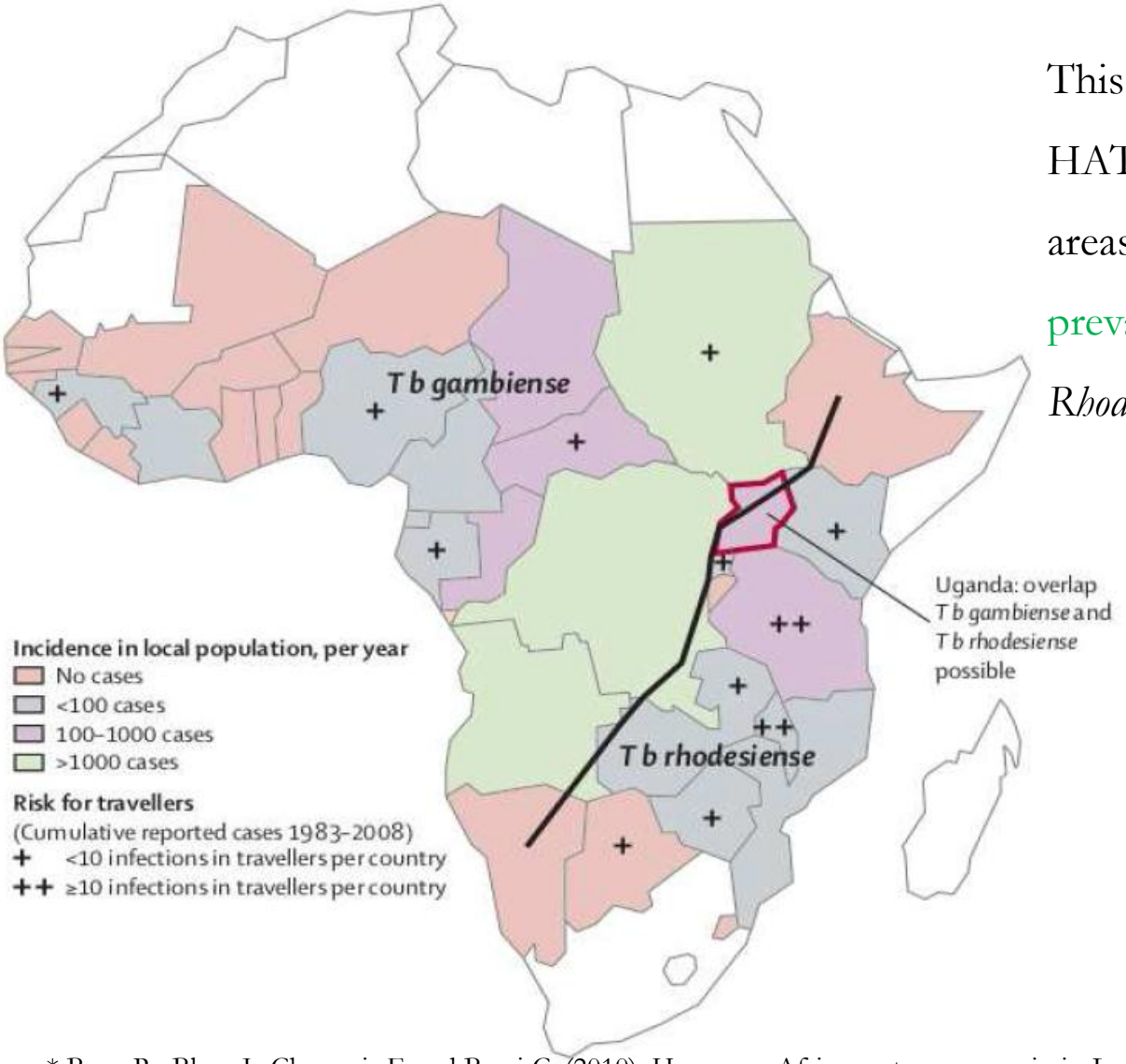
Human African trypanosomiasis (HAT) comprises two diseases:

1. Gambian HAT caused by Trypanosoma brucei gambiense found in West and Central Africa.

2. Rhodesian HAT caused by T. b. rhodesiense found in East and Southern Africa.

This presentation deals only with Rhodesian HAT

I.1. Human African trypanosomiasis in Africa*



This map shows the widespread of HAT. The solid line divides the areas in which *Gambian HAT* prevails and the areas where *Rhodesian HAT* predominates

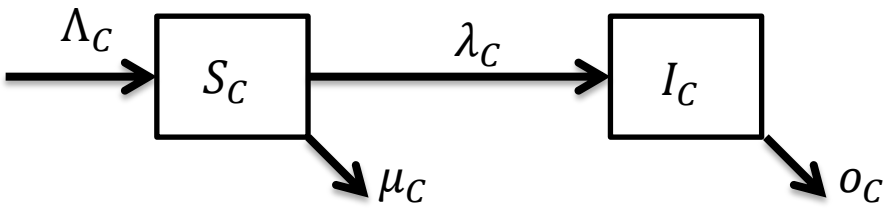
* Brun R., Blum J., Chappuis F. and Burri C. (2010), Human African trypanosomiasis, Lacent, 375, 148–159.

I.2. Control of Rhodesian HAT

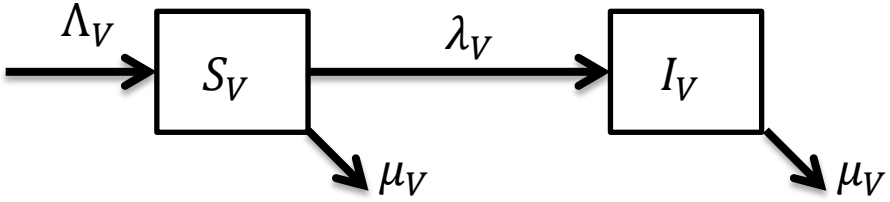
- Treatment of infected humans
- Treatment of cattle with Trypanocidal drugs (chemotherapy and chemoprophylaxis).
- Tsetse control:

  Insecticide-treated cattle, Baits, Targets, Aerial spraying, Ground spraying.

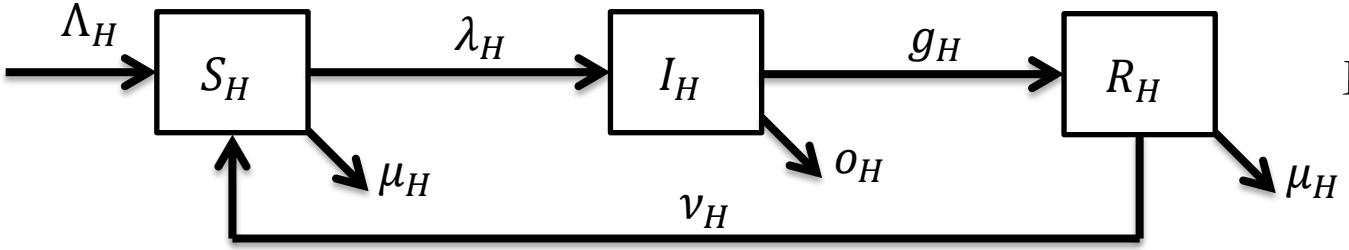
II. A basic model for trypanosomiasis transmission:



Cattle population



Tsetse flies



Human population

II.1. Model equations:

$$
\begin{cases}
\frac{d}{dt}S_H = \Lambda_H + \nu_H R_H - \mu_H S_H - \lambda_H(t-T_H)S_H(t-T_H) \\
\frac{d}{dt}I_H = \lambda_H(t-T_H)S_H(t-T_H) - (g_H+\sigma_H)I_H \\
\frac{d}{dt}R_H = g_H I_H - (\mu_H+\nu_H)R_H \\
\\
\frac{d}{dt}S_C = \Lambda_C - \mu_C S_C - \lambda_C(t-T_C)S_C(t-T_C) \\
\frac{d}{dt}I_C = \lambda_C(t-T_C)S_C(t-T_C) - \sigma_C I_C \\
\\
\frac{d}{dt}S_V = \Lambda_V - e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V S_V \\
\frac{d}{dt}I_V = e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V I_V
\end{cases}
$$

Recruitment and mortality rates

$$\mu_V = -\ln[q_C q_1 q_2^d + (1 - q_C) q_1 q_2^d]/d$$

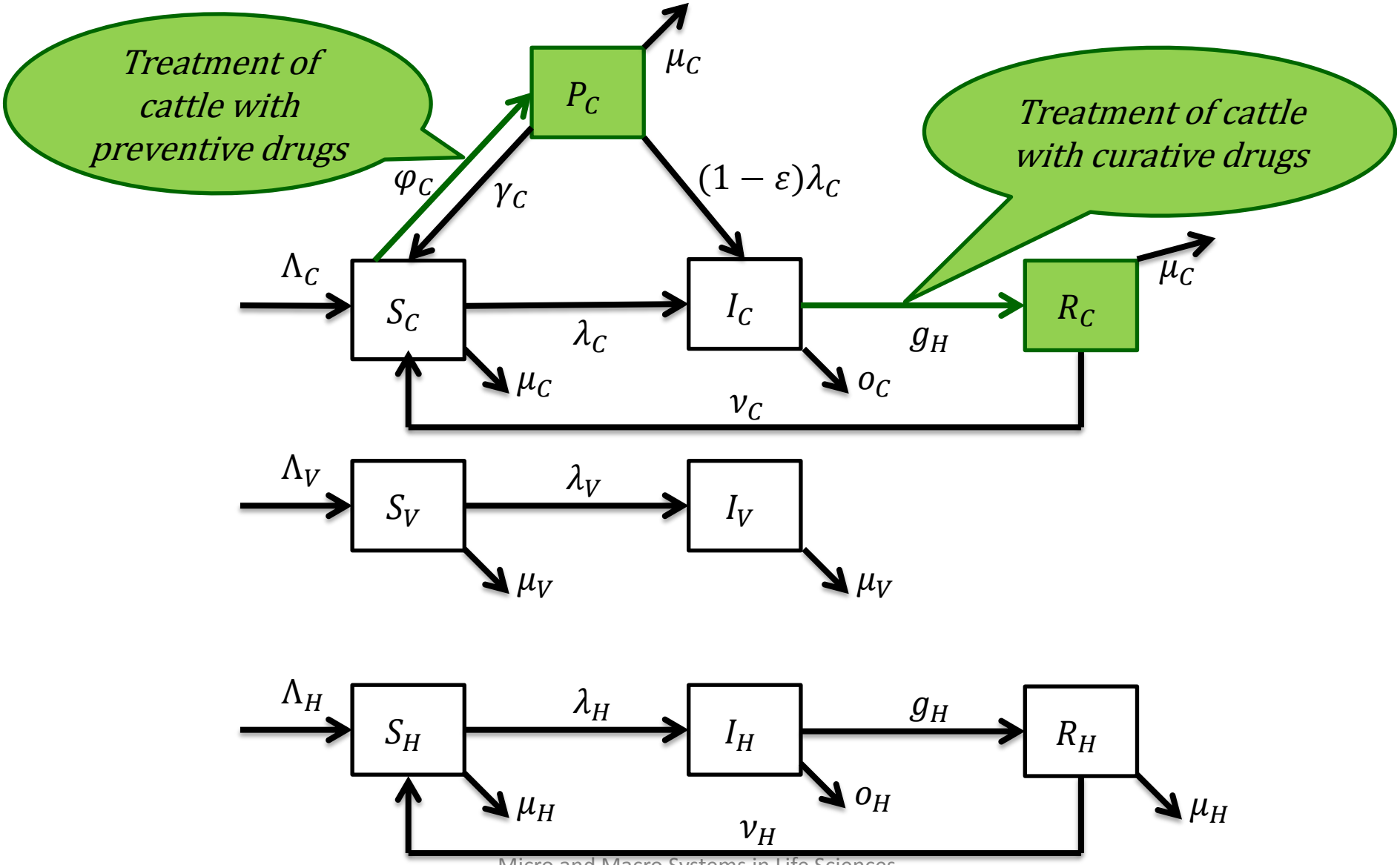
$$\Lambda_V = \frac{B_V}{(a + \mu_V)}(1 - e^{-(a+\mu_V)})$$

Force of infection

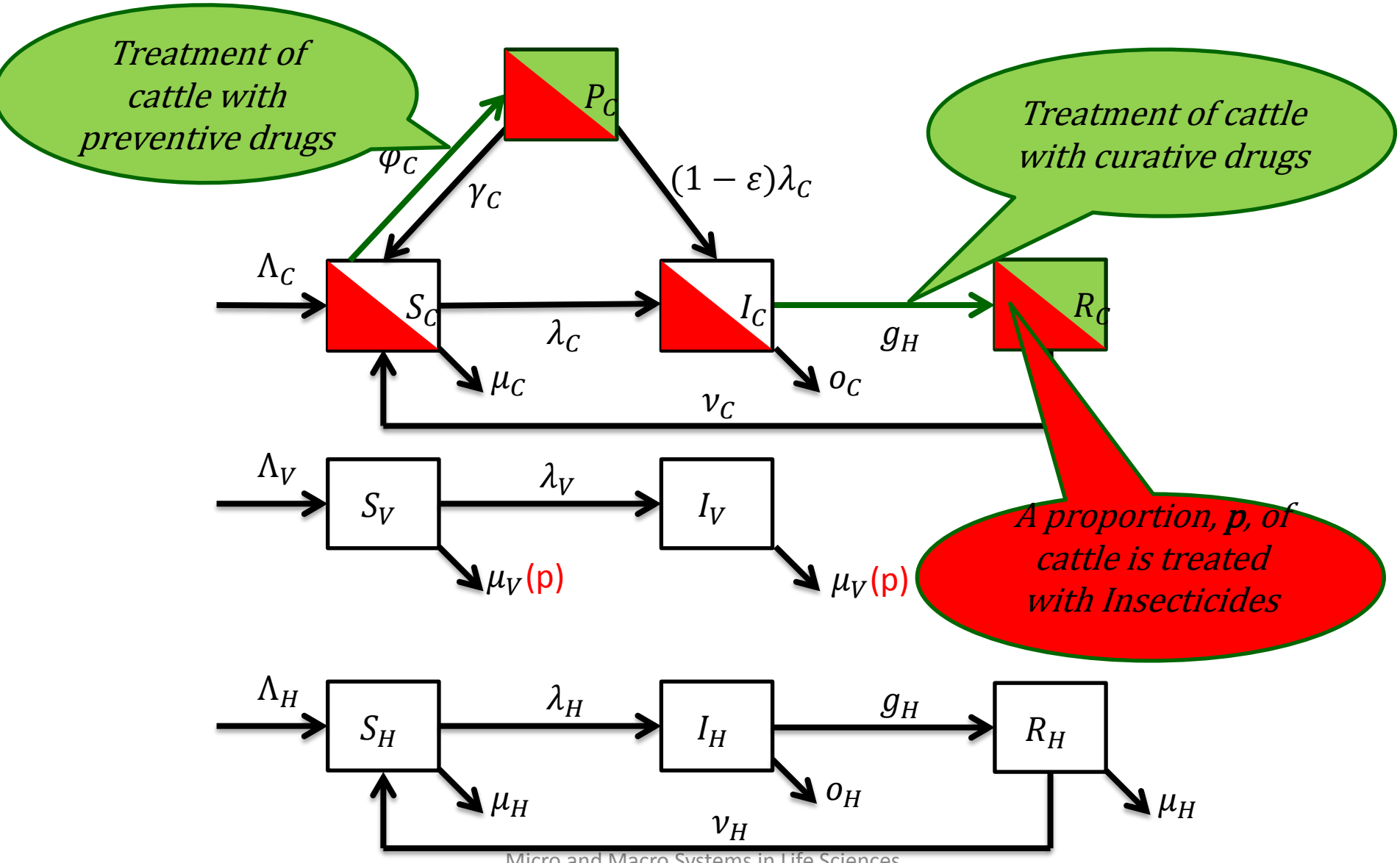
$$\lambda_H(t) = a_H \beta_H I_V(t)/N_H(t) \quad \lambda_C(t) = a_C \beta_C I_V(t)/N_C(t)$$

$$\lambda_V(t) = \alpha[a_H I_H(t)/N_H(t) + a_C I_C(t)/N_C(t)]$$

III. Adding trypanocides:



IV. Trypanocides and insecticides combined:



IV. 1. Mathematical Model

$$
\begin{cases}
\frac{d}{dt}S_H = \Lambda_H + \nu_H R_H - \mu_H S_H - \lambda_H(t-T_H)S_H(t-T_H) \\
\frac{d}{dt}I_H = \lambda_H(t-T_H)S_H(t-T_H) - (g_H+\sigma_H)I_H \\
\frac{d}{dt}R_H = g_H I_H - (\mu_H+\nu_H)R_H \\
\\
\frac{d}{dt}S_C = \Lambda_C + \nu_C R_C + \gamma_C P_C - \phi_C S_C - \mu_C S_C - \lambda_C(t-T_C)S_C(t-T_C) \\
\frac{d}{dt}P_C = \phi_C S_C - \mu_C P_C - \gamma_C P_C - (1-\epsilon)\lambda_C(t-T_C)P_C(t-T_C) \\
\frac{d}{dt}I_C = \lambda_C(t-T_C)[(1-\epsilon)P_C(t-T_C) + S_C(t-T_C)] - g_C I_C - \sigma_C I_C \\
\frac{d}{dt}R_C = g_C I_C - (\mu_C+\nu_C)R_C \\
\\
\frac{d}{dt}S_V = \Lambda_V(p) - e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V(p)S_V \\
\frac{d}{dt}I_V = e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V(p)I_V
\end{cases}
$$

Effect of insecticide treated cattle:

$$\mu_V(p) = -\ln[(1-p)q_C q_1 q_2^d + (1-q_C)q_1 q_2^d]/d$$

$$\Lambda_V(p) = \frac{B_V}{(a+\mu_V(p))}(1-e^{-(a+\mu_V(p))})$$

IV. 2. Mathematical analysis

Disease Free Equilibrium

$$E_0 = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, \frac{\Lambda_C(\mu_C + \gamma_C)}{\mu_C(\mu_C + \gamma_C + \phi_C)}, \frac{\phi_C \Lambda_C}{\mu_C(\mu_C + \gamma_C + \phi_C)}, 0, 0, \frac{\Lambda_V(p)}{\mu_V(p)}, 0 \right)$$

Basic Reproductive number R0

$$R_0 = \sqrt{R_{0H}^2 + R_{0C}^2}$$

$$R_{0H} = \sqrt{\frac{e^{-\mu_V(p)T_V} \Lambda_V(p) \alpha a_H^2 \mu_H \beta_H}{\mu_V^2(p) \Lambda_H (g_H + \sigma_H)}}$$

$$R_{0C} = \sqrt{\frac{e^{-\mu_V(p)T_V} \Lambda_V(p) \alpha a_C^2 \mu_C \beta_C (1 - \epsilon\pi)}{\mu_V^2(p) \Lambda_C (g_C + \sigma_C)}}$$

$$\pi = \frac{\phi_C}{(\phi_C + \mu_C + \gamma_C)}$$

IV. 3. Sensitivity analysis:

To determine how best one can reduce the burden of T. b. rhodesiense in both humans and cattle, it is necessary to know the relative importance of the control parameters of the model:

One way of achieving this is to calculate the the forward sensitivity index of R0 to the parameters of interest.

Definition:

The forward sensitivity index of R0 with respect to a parameter u is the ratio of the relative change in R0 to the relative change in u. This is given

$$\Gamma_u^{R0} = \frac{\frac{\Delta R0}{R0}}{\frac{\Delta u}{u}}$$

Taking the limit as $\Delta\mu$ tends to zero we obtain:

$$\Gamma_u^{R0} = \frac{\partial R0}{\partial u} * \frac{u}{R0}.$$

Using the models parameters' values we obtain

Parameter	Sensitivity index	Parameter	Sensitivity index
p	-1.2772	g_C	-0.3120
a_C	+0.9448	T	-0.2700
Λ_V	+0.500	σ_C	-0.1872
α	+0.500	a_H	+0.0044
μ_C	+0.4992	μ_H	+0.0008
β_C	+0.4992	β_H	+0.0008
B_C	-0.4992	B_H	-0.0008
ϵ	-0.3328	g_H	-0.0006
Φ_C	-0.3328	σ_H	-0.0002

This table demonstrates that the parameter p (proportion of ITC) has the highest negative impact on R0.

An increase of 1% in p would result in a decrease 0.3898% in R0.

As for ϕ_C we can see that an increase of 1% in this parameter will result in 0.0879% decrease in R0 which around four times less than that resulting from 1% decrease in p.

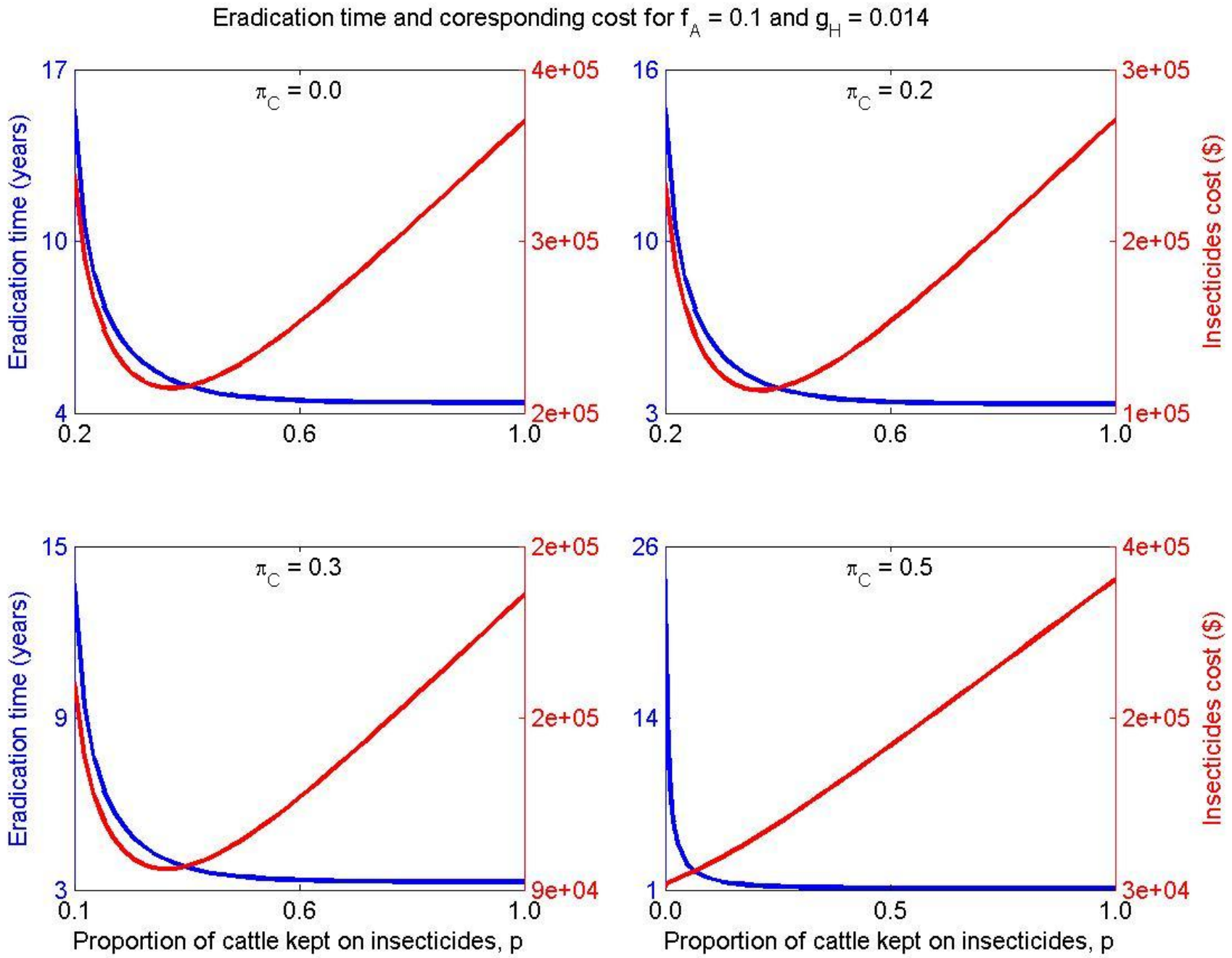
IV. 4. Model's simulations

Hargrove et al. (2012)

Using this model, Hargrove et al. (2012) estimated that trypanosomiasis can be eradicated
if 15% of cattle are treated with insecticides compared to 65% that needs to be treated
with trypanocides.

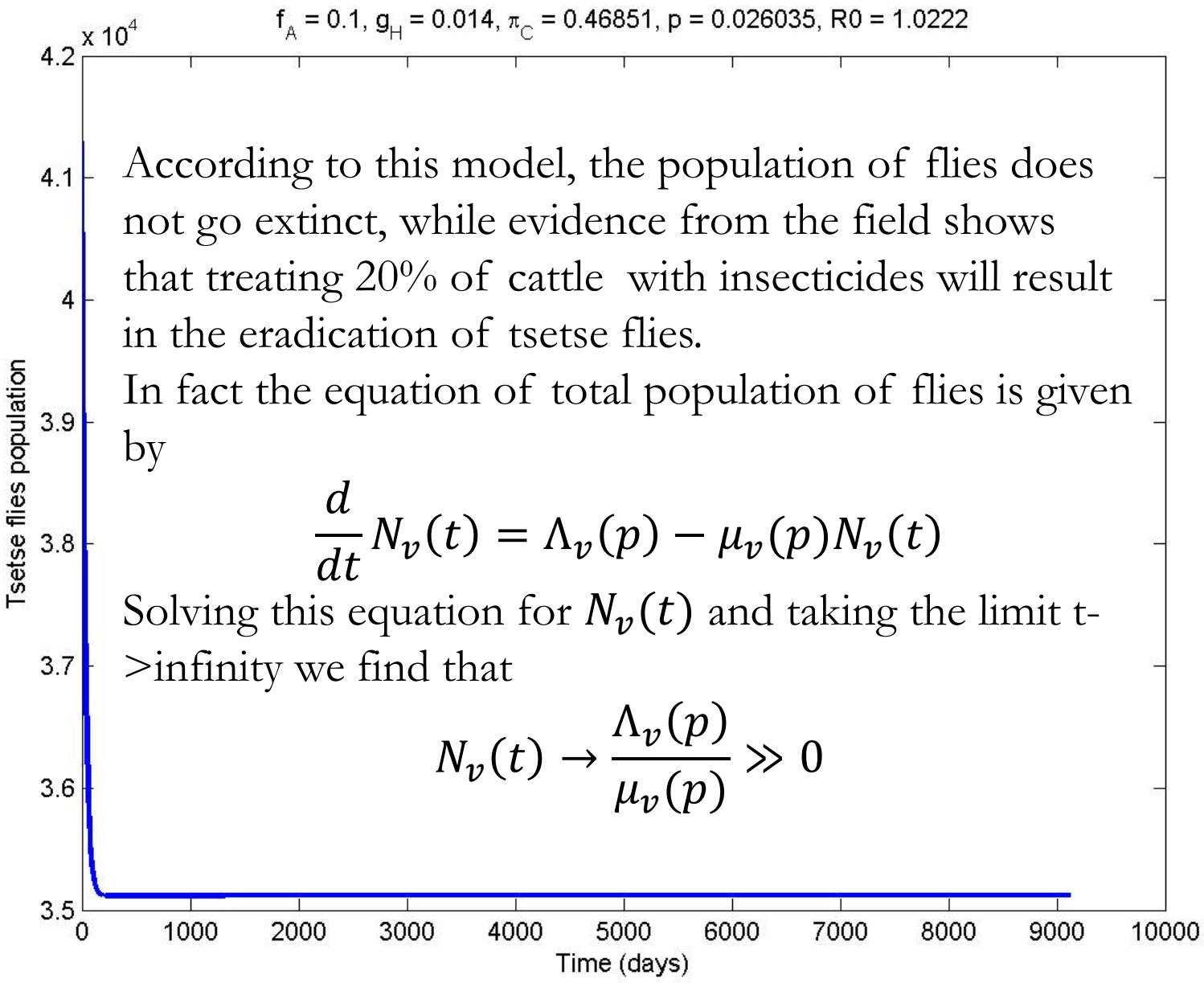
Kajunguri et al. (to be submitted)

In Kajunguri et al. (in progress), we estimated time to eradication and corresponding cost using Matlab solver "**dde23**" with "**event location**" option to determine the time to eradication.


Eradication time and coresponding cost for f_A = 0.1 and g_H = 0.014
π_C = 0.0
π_C = 0.2
π_C = 0.3
π_C = 0.5
Eradication time (years)
Insecticides cost ($)
Proportion of cattle kept on insecticides, p
17
10
4
16
10
3
15
9
3
26
14
1
4e+05
3e+05
2e+05
3e+05
2e+05
1e+05
2e+05
2e+05
9e+04
4e+05
2e+05
3e+04
0.2
0.6
1.0
0.1
0.0
0.5

This is all good and well.

BUT



According to this model, the population of flies does not go extinct, while evidence from the field shows that treating 20% of cattle with insecticides will result in the eradication of tsetse flies.

In fact the equation of total population of flies is given by

$$\frac{d}{dt}N_v(t) = \Lambda_v(p) - \mu_v(p)N_v(t)$$

Solving this equation for $N_v(t)$ and taking the limit t->infinity we find that

$$N_v(t) \to \frac{\Lambda_v(p)}{\mu_v(p)} \gg 0$$

What went wrong and how can we fix it?

Dead flies do not reproduce!!!

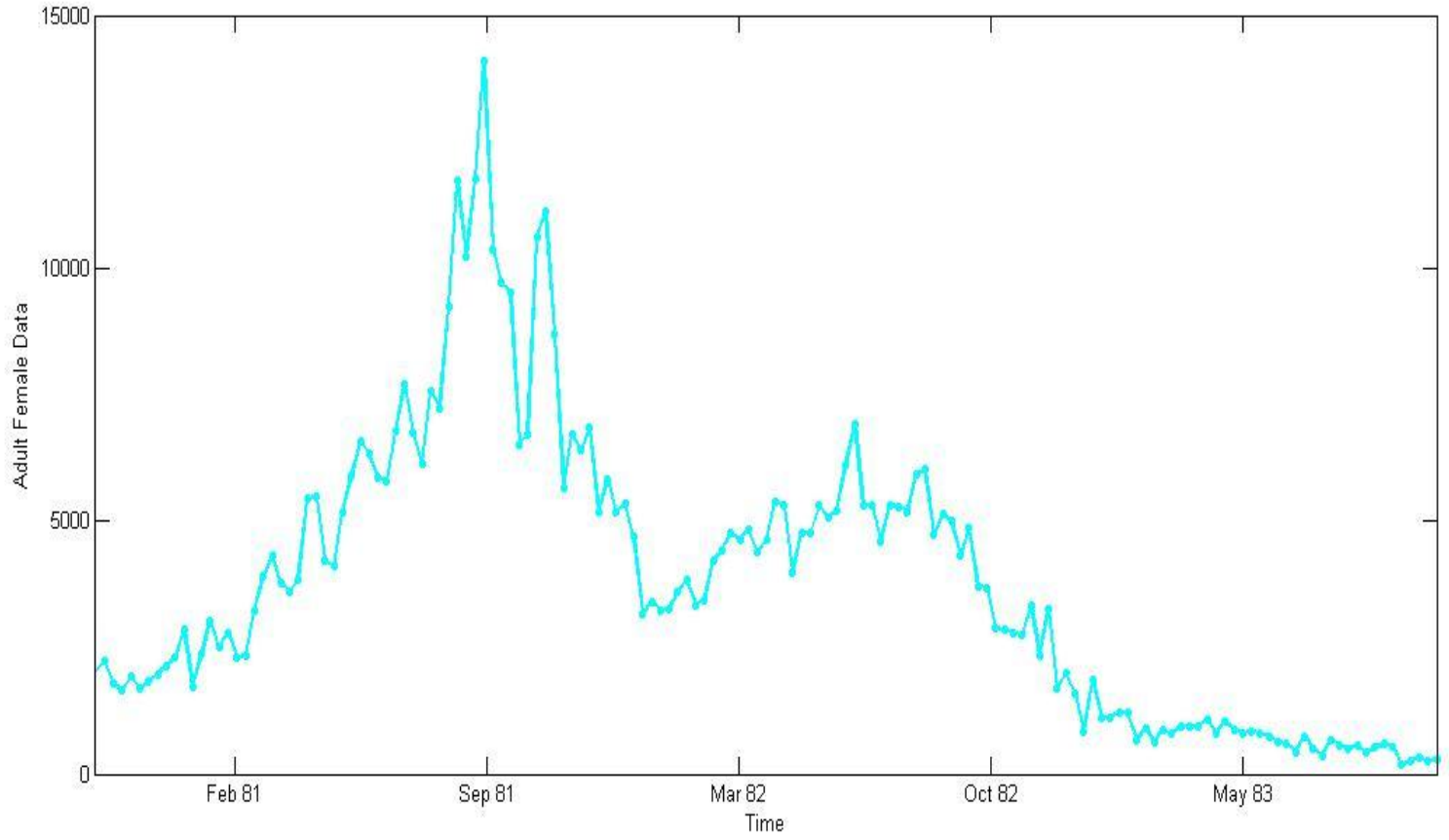
The above model assumed a constant birth rate implying that even if a high level of insecticides are applied and even if flies feed only on cattle (leading to fly eradication), the number of new births, $\Lambda_v(p)$, stays significantly high.

This suggests replacing the constant birth rate, $\Lambda_v(p)$, by a linear one; $\Lambda_v(p)N_v(t)$

The resulting tsetse equation becomes $\frac{d}{dt}N_v(t) = (\Lambda_v(p) - \mu_v(p))N_v(t)$

Another problem ☹

The resulting model predicts either exponential growth or extinction while data from Antelope Island (for example) show a stable growth.



V. Including fly density-dependency

V.1. A density dependent model for tsetse flies dynamics

$$\frac{d}{dt}P = bA - (\mu_P + cP(t))P(t) - \alpha P(t)$$

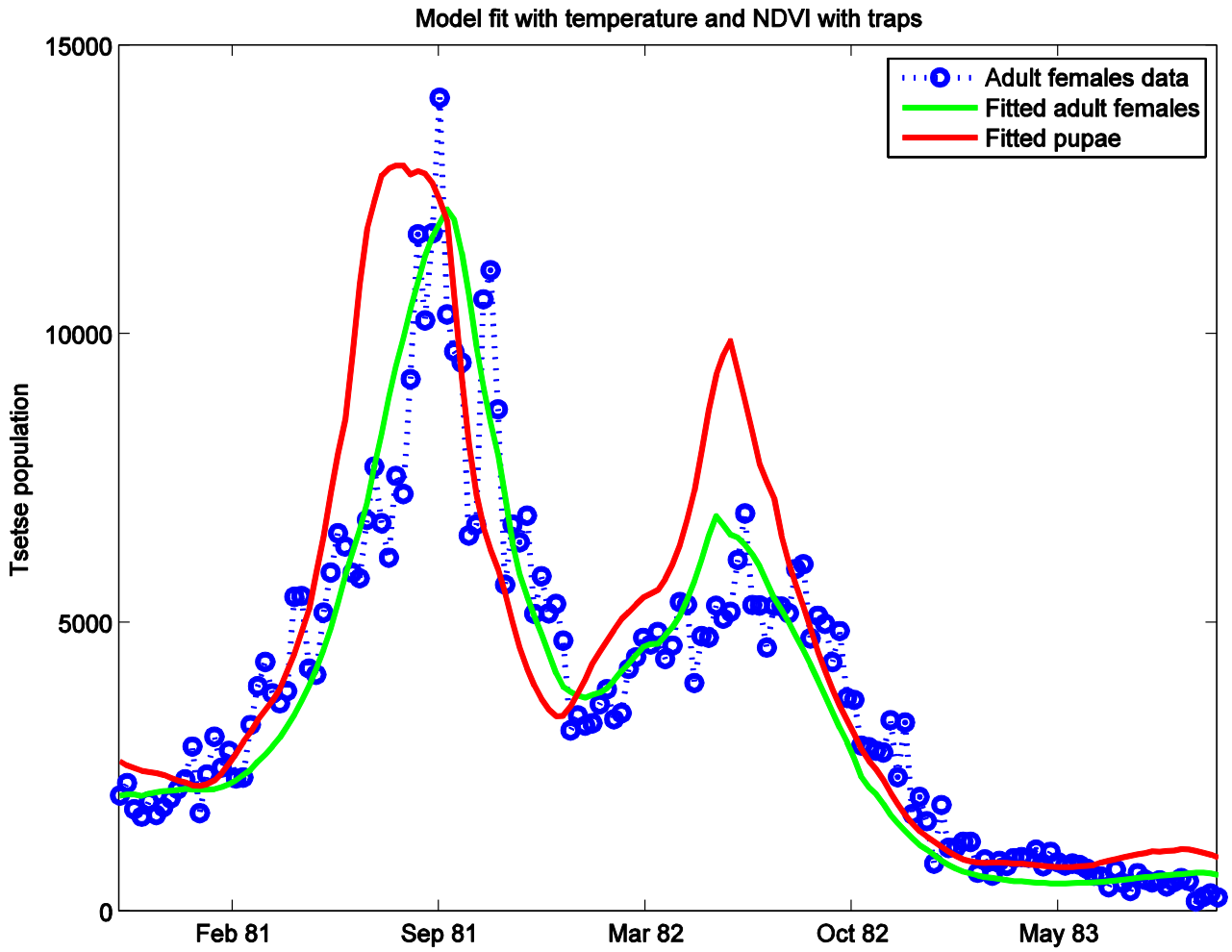
$$\frac{d}{dt}A = \alpha P - \mu_A A$$

With temperature and NDVI

$$\frac{d}{dt}P(t) = bA(t) - (\mu_P + c_1 e^{-c_2 NDVI(t)} P(t))P(t) - \alpha\left(T\left(t\right)\right)P(t)$$

$$\frac{d}{dt}A(t) = \alpha\left(T\left(t\right)\right)P - \left[\mu_A\left(T\left(t\right)\right) + Traps(t) + Target(t)\right]A$$

V.2. Tsetse model fit to data



V. 3. Trypanosomiasis model with density-dependency

$$
\begin{aligned}
\frac{d}{dt}S_H(t) &= \Lambda_H + \nu_H R_H - \mu_H S_H - \lambda_H S_H \\
\frac{d}{dt}I_H(t) &= \lambda_H S_H - (g_H + \sigma_H) I_H \\
\frac{d}{dt}R_H(t) &= g_H I_H - (\mu_H + \nu_H) R_H \\
\frac{d}{dt}S_C(t) &= \Lambda_C + \nu_C R_C + \gamma_C P_C - (\mu_C + \varphi_C) S_C - \lambda_C S_C \\
\frac{d}{dt}P_C(t) &= \varphi_C S_C - (\mu_C + \gamma_C) P_C - (1-\varepsilon)\lambda_C P_C \\
\frac{d}{dt}I_C(t) &= \lambda_C [(1-\varepsilon) P_C + S_C] - (g_C + \sigma_C) I_C \\
\frac{d}{dt}R_C(t) &= g_C I_C - (\mu_C + \nu_C) R_C \\
\frac{d}{dt}S_V(t) &= \Lambda_V N_V - K N_V S_V - e^{-\mu_V T_V} \lambda_V (t - T_V) S_V (t - T_V) - \mu_V S_V \\
\frac{d}{dt}I_V(t) &= e^{-\mu_V T_V} \lambda_V (t - T_V) S_V (t - T_V) - \mu_V I_V - K N_V I_V
\end{aligned}
$$

Density- dependent term

Linear birth rate

V.3.1. Mathematical analysis

Disease Free equilibrium PointSSSSS

The flies population is then modeled by the following logistic equation

$$\frac{d}{dt}N_V(t) = (\Lambda_V(p) - \mu_V(p) - KN_V)\,N_V$$

The growth rate of tsetse flies is then

$$r(p) := \Lambda_V(p) - \mu_V(p)$$

clearly when $r(p) < 0$, the population of flies goes extinct and the model only DFE is

$$\begin{cases} S_H^0 = \dfrac{\Lambda_H}{\mu_H} \\ S_C^0 = \dfrac{\Lambda_C(\mu_C + \gamma_C)}{\mu_C(\mu_C + \gamma_C + \varphi_C)} \\ P_C^0 = \dfrac{\varphi_C \Lambda_C}{\mu_C(\mu_C + \gamma_C + \varphi_C)} \\ S_V^0 = 0 \end{cases}$$

when $r(p) > 0$ the flies population stabilies at its maximal carrying capacity

$$N_V := \frac{\Lambda_V(p) - \mu_V(p)}{K}$$

and an additional DFE exists

$$\begin{cases} S_H^0 = \dfrac{\Lambda_H}{\mu_H} \\ S_C^0 = \dfrac{\Lambda_C\left(\mu_C + \gamma_C\right)}{\mu_C\left(\mu_C + \gamma_C + \varphi_C\right)} \\ P_C^0 = \dfrac{\varphi_C \Lambda_C}{\mu_C\left(\mu_C + \gamma_C + \varphi_C\right)} \\ S_V^0 = \dfrac{\Lambda_V(p) - \mu_V(p)}{K} \end{cases}$$

Basic Reproductive number:

$$R_0 = \sqrt{R_{0H}^2 + R_{0C}^2}$$

where

$$R_{0H} := \sqrt{\frac{e^{-\mu_V(p)T_V} S_V^0 \alpha a_H}{S_H^0 (g_H + \sigma_H)} \frac{a_H \beta_H}{\mu_V(p) + K S_V^0}}$$

$$R_{0C} := \sqrt{\frac{e^{-\mu_V(p)T_V} S_V^0 \alpha a_C}{S_C^0 (g_C + \sigma_C)} \frac{a_C \beta_C \left[(1-\varepsilon) P_C^0 + S_C^0\right]}{S_C^0 (\mu_V(p) + K S_V^0)}}.$$

This model does indeed predict flies eradication when p>p* with p* being the critical value that satisfies R0=1.

The model is then used to estimate, for each value of p>p*, the time to eradication and corresponding costs. Figures not shown here.

V.4. Model's key findings

With this model, insecticides based intervention can choose between:

1. Eradicating tsetse flies by increasing p; until $r(p) < 0$.
2. If this not practical, too costly, or one just wants to be nice to flies, interventions can aim at eradicating the disease while preserving the population of uninfected flies.

   This can be achieved by bringing R0 bellow 1 while keeping $r(p)>0$.

VI. Model with open populations (to fly immigration)

$$
\begin{aligned}
\frac{d}{dt}S_H(t) &= \Lambda_H + \nu_H R_H - \mu_H S_H - \lambda_H S_H \\
\frac{d}{dt}I_H(t) &= \lambda_H S_H - (g_H + \sigma_H)\, I_H \\
\frac{d}{dt}R_H(t) &= g_H I_H - (\mu_H + \nu_H)\, R_H \\
\frac{d}{dt}S_C(t) &= \Lambda_C + \nu_C R_C + \gamma_C P_C - (\mu_C + \varphi_C)\, S_C - \lambda_C S_C \\
\frac{d}{dt}P_C(t) &= \varphi_C S_C - (\mu_C + \gamma_C)\, P_C - (1-\varepsilon)\, \lambda_C P_C \\
\frac{d}{dt}I_C(t) &= \lambda_C\, [(1-\varepsilon)\, P_C + S_C] - (g_C + \sigma_C)\, I_C \\
\frac{d}{dt}R_C(t) &= g_C I_C - (\mu_C + \nu_C)\, R_C \\
\frac{d}{dt}S_V(t) &= (1-f)\Omega_V + \Lambda_V N_V - K N_V S_V - e^{-\mu_V T_V} \lambda_V\, (t - T_V)\, S_V\, (t - T_V) - \mu_V S_V \\
\frac{d}{dt}I_V(t) &= f\Omega_V + e^{-\mu_V T_V} \lambda_V\, (t - T_V)\, S_V\, (t - T_V) - \mu_V I_V - K N_V I_V
\end{aligned}
$$

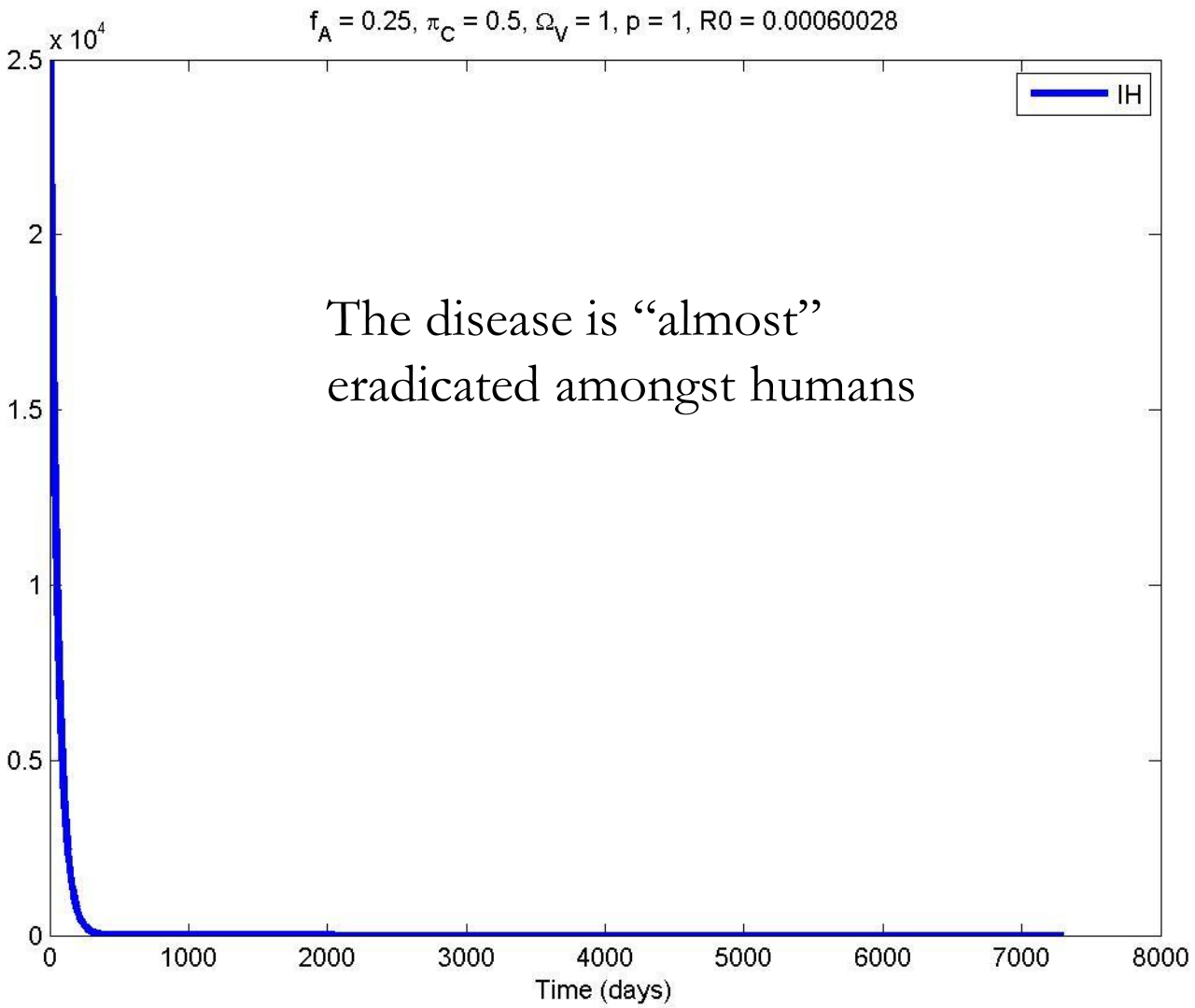
VI.1. Model's key findings

- This is where the mathematical tools reach their limit.

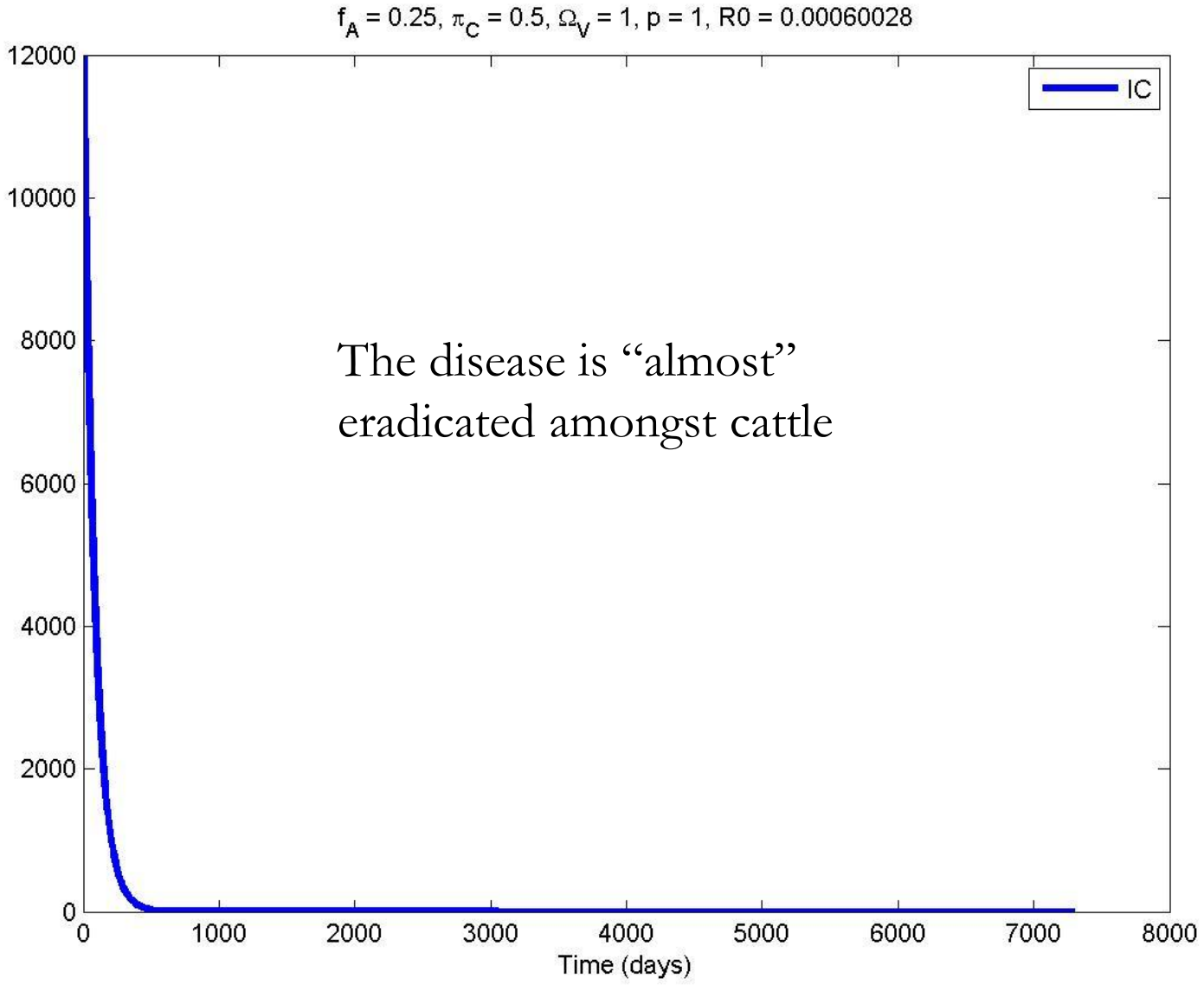
  No DFE and therefore, **No R0**.

- **No DFE** then eradication is **not possible** in open populations.
- However, the disease can be controlled as suggested by the model's simulations

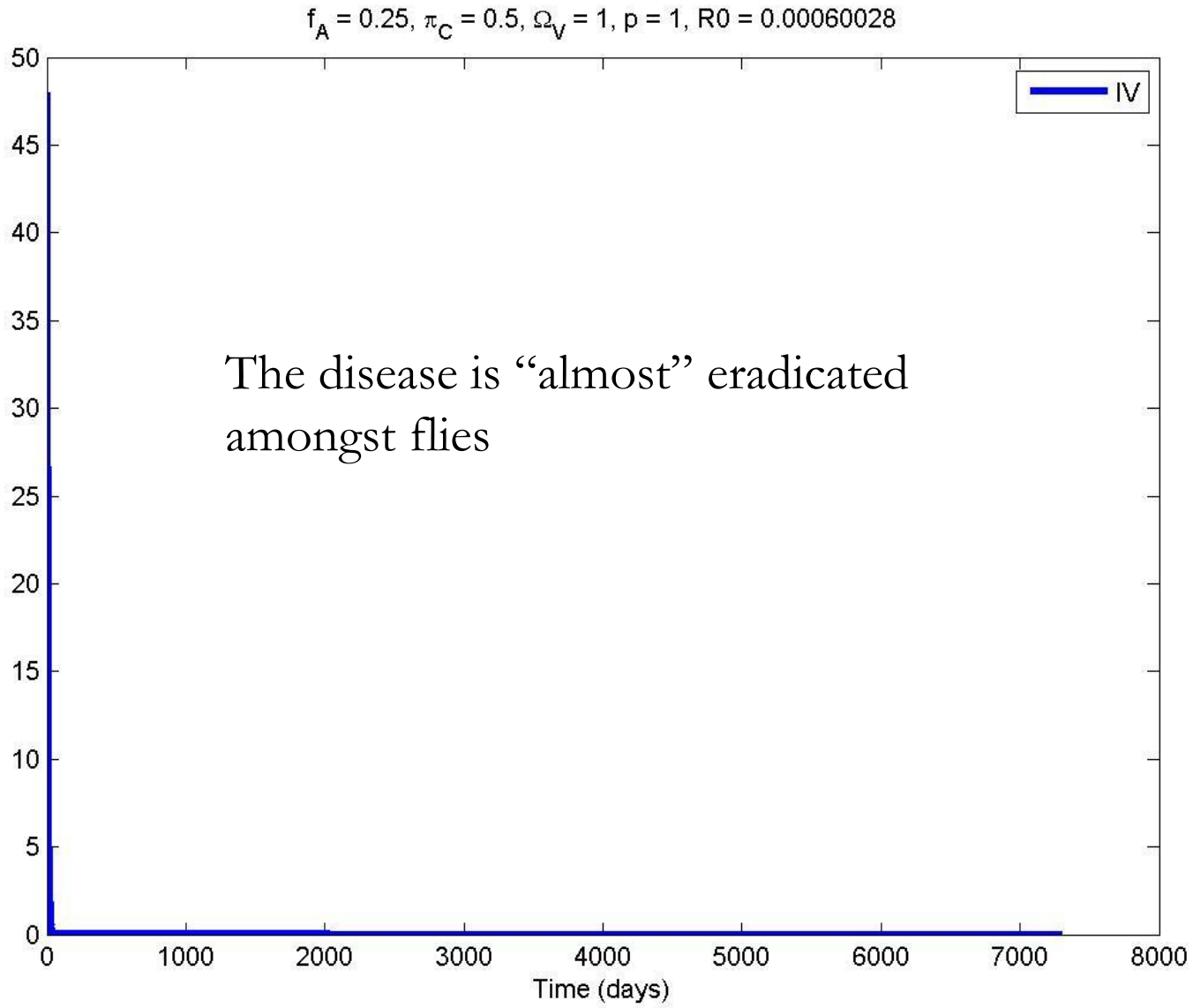
Model Simulation



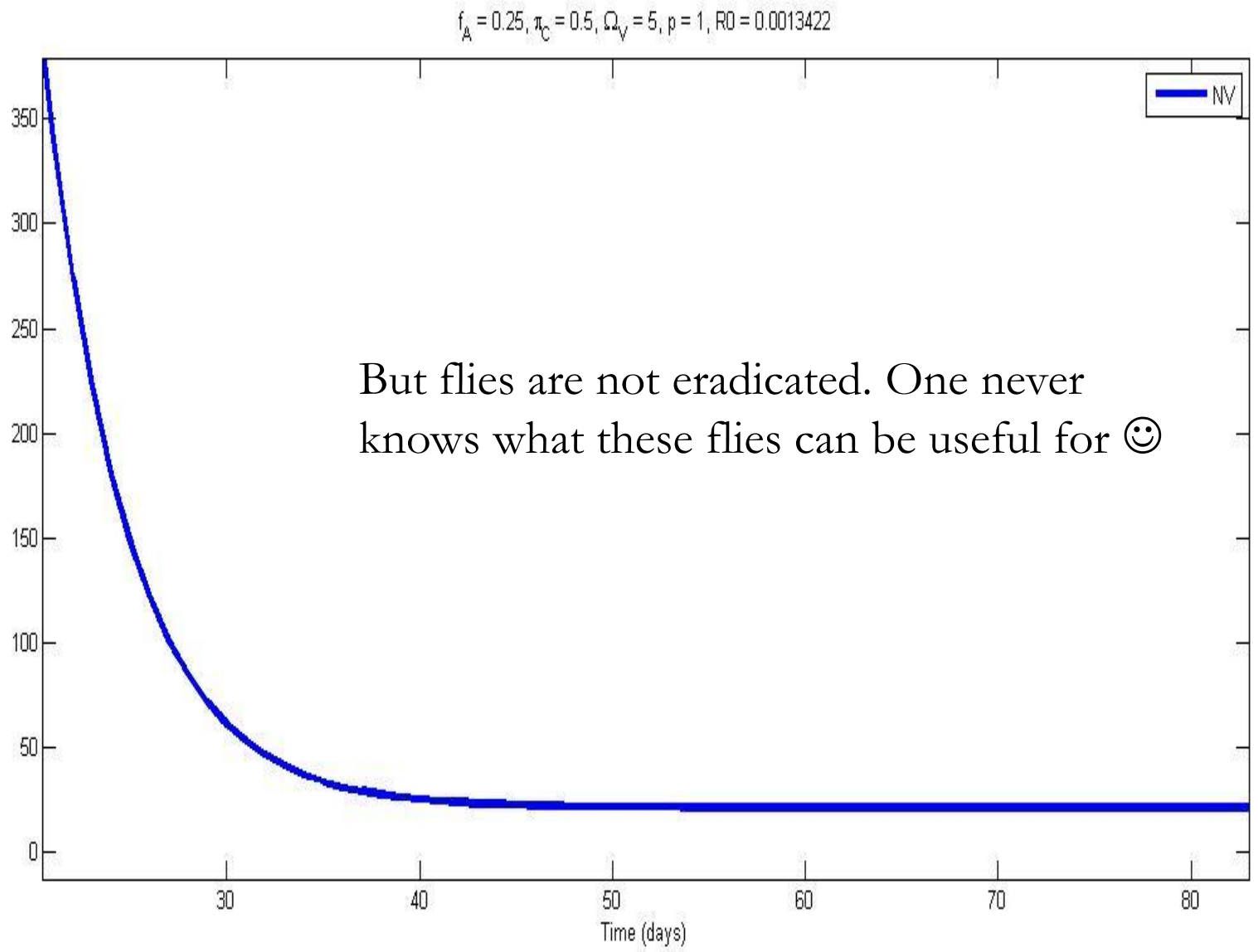
The disease is "almost" eradicated amongst humans



The disease is "almost" eradicated amongst cattle



The disease is "almost" eradicated amongst flies



But flies are not eradicated. One never knows what these flies can be useful for ☺

VII. Conclusion:

- This model confirms (what we already know) that, in open populations, eradication of trypanosomiasis is **not possible** with the use of trypanocides and insecticides only.
- Disease eradication can be achieved if immigration of flies is stopped completely (using treated traps and baits, etc.. at the "border" of the affected area).
- Otherwise, control of the disease can be achieved if high levels of insecticides and/or trypanocides are implemented and maintained.

In progress: Time-dependent controls:

$$
\begin{cases}
\frac{d}{dt}S_h = & B_h + \nu_h R_h - \mu_h S_h - \beta_h S_h \\
\frac{d}{dt}I_h = & \beta_h S_h - \rho_h u_1(t) I_h - \sigma_h I_h \\
\frac{d}{dt}R_h = & (\rho_{0h} + \rho_h u_1(t))\, I_h - \mu_h R_h - \nu_h R_h \\
 & \\
\frac{d}{dt}S_{cu} = & B_{cu} + \nu_c R_{cu} + \gamma S_{ct} - \mu_c S_{cu} - \beta_c S_{cu} - u_3(t) S_{cu} \\
\frac{d}{dt}I_{cu} = & \beta_c S_{cu} + \gamma I_{ct} - \rho_c u_2(t) I_{cu} - \sigma_c I_{cu} - u_3(t) I_{cu} \\
\frac{d}{dt}R_{cu} = & (\rho_{0c} + \rho_c u_2(t))\, I_{cu} + \gamma R_{ct} - \mu_c R_{cu} - \nu_c R_{cu} - u_3(t) R_{cu} \\
 & \\
\frac{d}{dt}S_{ct} = & B_{ct} + \nu_c R_{ct} - \mu_c S_{ct} - \beta_c S_{ct} - \gamma S_{ct} + u_3(t) S_{cu} \\
\frac{d}{dt}I_{ct} = & \beta_c S_{ct} - \rho_c I_{ct} - \sigma_c I_{ct} - \gamma I_{ct} + u_3(t) I_{cu} \\
\frac{d}{dt}R_{ct} = & (\rho_{0c} + \rho_c)\, I_{ct} - \mu_c R_{ct} - \nu_c R_{ct} - \gamma R_{ct} + u_3(t) R_{cu} \\
 & \\
\frac{d}{dt}S_v = & \Lambda_v(t) - \lambda S_v - \mu_v(t) S_v \\
\frac{d}{dt}I_v = & \lambda S_v - \mu_v(t) I_v
\end{cases}
$$

where

$$\mu_v(t) = -\frac{\ln\left(q_f q_n^d\right)}{d} + \sum_{k=0}^{E\left(\frac{t}{d}\right)} \frac{P\left(t-kd\right) - P\left(t-(k+1)\,d\right)}{\int_{t-(k+1)d}^{t-kd} \left(1 - P\left(\tau\right)\right) d\tau}$$

with

$P\left(\tau\right) := \dfrac{N_{ct}\left(\tau\right)}{N_{ct}\left(\tau\right) + N_{cu}\left(\tau\right)}$ is the proportion of cattle treated with insecticides at time τ.

This leads to an integro-differential equation with multiple delays for which an optimal control problem needs to be formulated.

Any ideas are most welome??

Thank you