

A Reservoir Model of Chagas Disease

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Abstract

More than 1 billion people all over the world are infected with neglected tropical diseases, such as Chagas disease in Latin and South America. Like malaria, this disease is passed between infected animals and people by an insect, the reduviid bug. In this paper, an ordinary differential equations model was developed that accounts for the existence of a disease reservoir in mammals, such as domestic livestock. Our results show that the disease free state is not a stable equilibrium, meaning that the introduction of even a small number of insects will lead to an epidemic.

1 Introduction

More than 1 billion people all over the world are infected with neglected tropical diseases, such as: Cysticercosis, Dengue fever, Leprosy, Human African Trypanosomiasis, Yaws, Trachoma, and Chagas disease, to name just a few. One of the most common of these is Chagas disease[2].

Between 8 and 11 million people in Latin and South America have Chagas disease and about 20,000 die annually from the disease[2]. Chagas disease is also known as American Typanosomiasis because of its similarity to African Trypanosomiasis (African Sleeping Sickness). The primary difference between these two diseases is location. Chagas disease is found in Central America, South America, Mexico, and recently the United States, mainly in Texas. The countries included in this region are: Mexico, Brazil, Chile, Uruguay, Bolivia, Argentina, Peru, El Salvador, Honduras, Paraguay, Guatemala, Ecuador, Venezuela, Columbia, Costa Rica, Panama, and Nicaragua(See Figure 1). As the name suggests, African Trypanosomiasis is found in Africa, mainly the sub-saharan countries.

Carlos Chagas was a Brazilian scientist who first described Chagas disease in 1909 in Rio de Janeiro, Brazil, although it was not a major health concern until the 1960's. It is now known as an inflammatory, infectious condition caused by the parasite *Trypanosoma cruzi*[1]. This parasite is found in the feces of the *Triatoma sp.* insect, commonly known as the reduviid bug or kissing bugs. The reduviid bug ingests the parasite from other animals or people that are infected with it. Research has focused on



Figure 1: Left:Central America death rates per capita (2008). Right:South America death rates per capita(2008).

the reduviid bug biting humans, even though there is a vast reservoir of animals that it may infect including: opossums, armadillos, raccoons, monkeys, rats, coyotes, dogs, cats, and many others. Birds, amphibians, and reptiles are naturally resistant to it but can carry it and give it to the reduviid bugs. The parasite does not harm the health of livestock but they also can carry it[8]. When a reduviid bug bites a host, it ingests the host's blood and leaves behind its feces on the surface of the skin. The feces contain the parasite and this irritates the skin. Because of this irritation, the host tends to scratch or wipe at the bite, causing the parasite in the feces to enter into the body and spread then multiply.

The reduviid bugs are 0.75 to 1.5 inches in length[5]. They commonly live in mud, thatch, or adobe houses/huts and hide in crevices during the day. At night, they come out and feed on sleeping humans or animals, generally feeding on their faces, thus the name kissing bugs. It is rare, but not impossible, to get infected while traveling to impoverished rural areas in Latin or South America. Chagas disease is not only contracted through the reduviid bug, it can also be contracted from blood, for example being born of a woman with the *T.cruzi* parasite, blood transfusions, organ transplant, working in a lab dealing with Chagas disease testing[2].

Chagas is found most often in children and occurs in three stages: acute, latent, and chronic[1]. The acute stage lasts for weeks to months and induces mild symptoms that include: swelling at infection site, fever, fatigue, rash, aches, and nausea. The most common sign of acute Chagas disease is Romana's sign, which is swelling of the eyelids on the side of the face nearest to the bite or infection site[1]. If the infection goes untreated, it will continue on to the latent stage. The latent stage generally lasts 10 to 20 years and is asymptomatic, although the patients in this phase test positive with blood tests. Only about 10 percent of these patients continue on to the chronic stage[10]. Within the chronic stage,

symptoms include irregular heartbeat, congestive heart failure, cardiac arrest, enlarged esophagus and colon, and enlarged heart. These symptoms can prove to be fatal.

Prevention of this disease is simple: use nets and insecticides[1]. General avoidance of sleeping in mud, thatch, and adobe houses is ideal but not very applicable because it is readily available and cheap. Insecticides and netting have shown to have the most effect on preventing Chagas disease, especially nets sprayed with insecticides. Strategies for how to most efficiently spray these insecticides in varying areas are known and have been carried out affectively in countries such as Brazil, Chile, and Uruguay, and some progress has been made in Argentina, Bolivia, and Mexico as well[2]. However, plans are often not carried out to completion, due to political and economical reasons. A more economical approach is called for to better cater to these countries.

There are medicinal treatments available for Chagas disease. However, the effect of these drugs is temperamental, depending on the stage of the disease. There are two main drugs for this particular parasitic elimination: Benznidazole and Nifurtimox[1]. The younger one is and the lower the stage of infection, the greater chance of parasite elimination. With these drugs, there is about a 70 percent cure rate with those patients in the acute stage[10]. In the latent stage, it is thought that there is a high cure rate also, although data is somewhat incomplete. These medications are ineffective in the chronic stage.

This disease has not been mathematically modelled frequently in the past. One recent model of this disease was done in 2008 by Devillers, Lobry, and Menu [4] in which two strains of *Trypanosoma cruzi* were modelled stochastically at the level of the individual. They found the inclusion of the reservoir was necessary for obtaining realistic results. The ideas they put forward stimulated the creation of the model presented here.

2 Methods

A differential equation model was developed that incorporated each individual stage of Chagas disease; the rates at which the parasite goes from vector to host α , the rates at which the parasite goes from host to vector β , rate at which parasite goes from reservoir to vector θ , death rates from Chagas disease γ , and general birth μ and death rates δ of the human population and of the reduviid bug (See Figure 2). The rate from acute to latent stage α_l is set to 0.125 or 1/8 because it takes on average 8 weeks to transfer from the acute to the latent stage[11]. The rate from latent to chronic stage α_c is set to 0.0001 or $1/((10)(20)(52))$ because it takes 20 years to transfer from the latent to the chronic stage[11] and only about 10 % of the people in the latent stage go on to the chronic stage[cite]. The human death rate δ_p is based on a 65 year life expectancy, that is $0.000296=1/((65)(52))$ which is about 0.0003[4]. The bug death rate δ_b is based on a 20 week life expectancy, that is $0.05=1/20$ [7]. We also assume that the birth and death rates are the same or relatively close to the same in this study. The transmission rates from humans to insects would be the highest in the chronic stage so, we assume that $\beta_l = \beta_c/2$

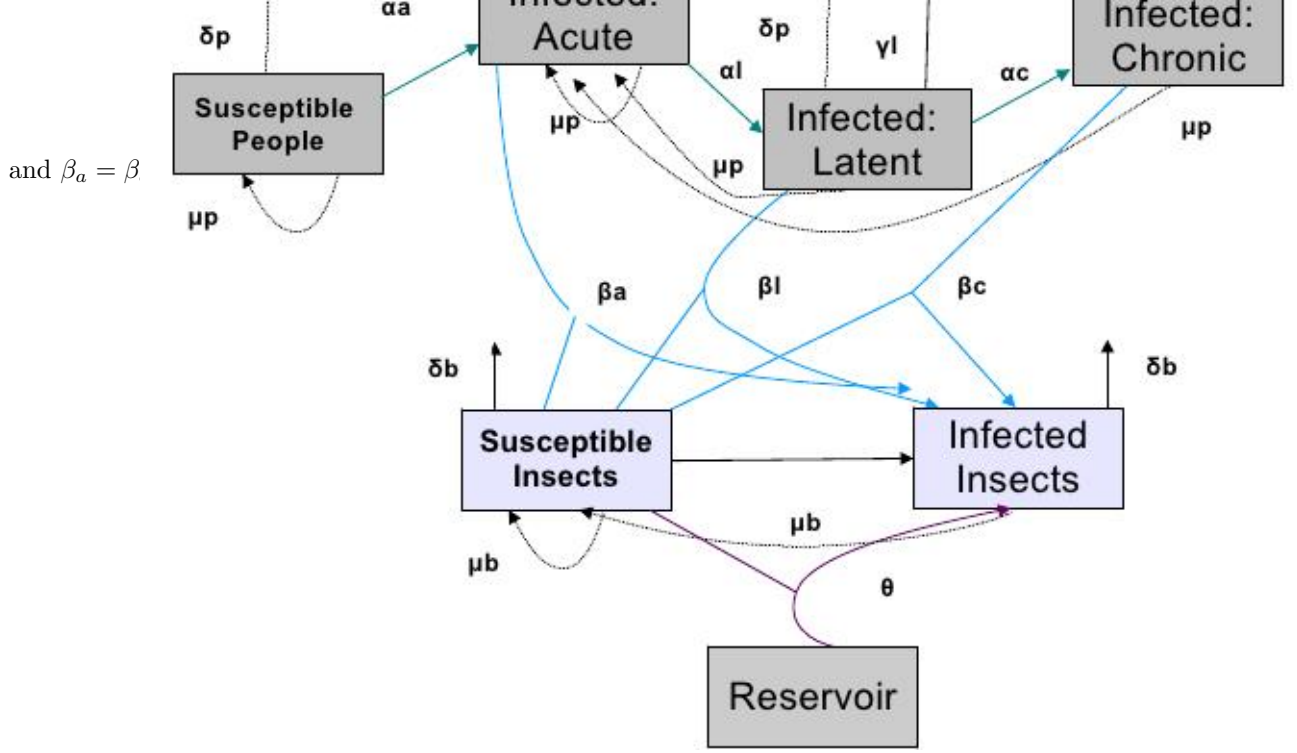


Figure 2: Transmission of Chagas disease

The following ordinary differential equations(ODE) model codifies these transmission paths.

$$\frac{dS_p}{dt} = -\alpha_a S_p I_b + \mu_p S_p - \delta_p S_p, \quad (1)$$

$$\frac{dI_{pa}}{dt} = \alpha_a S_p I_b - \alpha_l I_{pa} - \delta_p I_{pa} + \mu_p (I_{pa} + I_{pl} + I_{pc}) - \gamma_a I_{pa}, \quad (2)$$

$$\frac{dI_{pl}}{dt} = \alpha_l I_{pa} - \alpha_c I_{pl} - \delta_p I_{pl} - \gamma_l I_{pl}, \quad (3)$$

$$\frac{dI_{pc}}{dt} = \alpha_c I_{pl} - \delta_p I_{pc} - \gamma_c I_{pc}, \quad (4)$$

$$\frac{dS_b}{dt} = -\beta_a S_b I_{pa} - \beta_l S_b I_{pl} - \beta_c S_b I_{pc} + \mu_b (S_b + I_b) - \delta_b S_b - \theta S_b, \quad (5)$$

$$\frac{dI_b}{dt} = \beta_a S_b I_{pa} + \beta_l S_b I_{pl} + \beta_c S_b I_{pc} - \delta_b I_b + \theta S_b. \quad (6)$$

There are six populations considered: susceptible people S_p , susceptible insects S_b , infected people in the acute stage I_{pa} , infected people in the latent stage I_{pl} , infected people in the chronic stage I_{pc} , and infected insects I_b (See Equations (1-6)). We assume that all births by infected mothers result in an infected child in the acute stage[12] and that births by infected bugs result in susceptible bugs [5].

The matrix of partial derivatives of the ODE equations, the Jacobian, is used to identify stable states of the system: when all the eigenvalues are negative, the state is stable.

Table 1: Parameters

Parameter	Description	Value	Source
α_a	Transmission rate from insect to human	?	
α_l	Rate from acute to latent stage	0.125	Prata (2001)
α_c	Rate from latent to chronic stage	0.0001	Prata (2001)
β_a	Transmission rate human to insect: acute	$\beta_c/4$	This study
β_l	Transmission rate human to insect: latent	$\beta_c/2$	This study
β_c	Transmission rate human to insect: chronic	?	
γ_a	Human mortality from the acute stage	0.00003	Sanchez-Guillen (2006)
γ_l	Human mortality from the latent stage	0.00001	Devillers (2008)
γ_c	Human mortality from the chronic stage	0.0005	Prata (2001)
δ_p	Human death rate from other causes	0.0003	Devillers (2008)
δ_b	Insect death rate	0.05	Canals (1991)
μ_p	Human birth rate	0.000323	This study
μ_b	Insect birth rate	0.05	This study
θ	Transmission rate from reservoir to insect	?	

$-\alpha_a I_b + \mu_p - \delta_p$	0	0	0	0	$-\alpha_a S_a$
$\alpha_a I_b$	$-\alpha_l - \delta_p + \mu_p - \gamma_a$	μ_p	μ_p	0	$\alpha_a S_a$
0	α_l	$-\alpha_c - \delta_p - \gamma_l$	0	0	0
0	0	α_c	$-\delta_p - \gamma_c$	0	0
0	$-\beta_a S_b$	$-\beta_l S_b$	$-\beta_c S_b$	$-\beta_a I_{pa} - \beta_l I_{pl} - \beta_c I_{pc} + \mu_b - \delta_b - \theta$	μ_b
0	$\beta_a S_b$	$\beta_l S_b$	$\beta_c S_b$	$\beta_a I_{pa} + \beta_l I_{pl} + \beta_c I_{pc} + \theta$	δ_b

Euler's method was used to approximate solutions to the ODE's. A continuous time stochastic model(See Table 2) was also developed, based on this ODE model, using the Gillespe algorithm [9] as this may be more accurate at low levels of infection. All models were implemented in C [3] and graphics were generated using Stata[13].

Table 2: Stochastic Model Equations

	Equation	Event
a_1	$\mu_p S_p$	Birth for S_p
a_2	$\delta_p S_p$	Death for S_p
a_3	$\alpha_a S_p I_b$	Initial infection
a_4	$\mu_p (I_{pa} + I_{pl} + I_{pc})$	Birth for I_p
a_5	$\delta_p I_{pa} + \gamma_a I_{pa}$	Death for I_{pa}
a_6	$\alpha_l I_{pa}$	Transition from I_{pa} to I_{pl}
a_7	$\delta_p I_{pl} + \gamma_l I_{pl}$	Death for I_{pl}
a_8	$\alpha_c I_{pl}$	Transition from I_{pl} to I_{pc}
a_9	$\delta_p I_{pc} + \gamma_c I_{pc}$	Death for I_{pc}
a_{10}	$\mu_b (S_b + I_b)$	Birth for S_b
a_{11}	$\delta_b S_b$	Death for S_b
a_{12}	$\beta_a S_b I_{pa} + \beta_l S_b I_{pl} + \beta_c S_b I_{pc} + \theta S_b$	Infection of Insect
a_{13}	$\delta_b I_b$	Death for I_b

3 Results

Devillers [4] parameters were initially used and found to give completely unrealistic results in that the initial susceptible populations immediately became infected and the entire human population died. For example, a big α and a small β will have a basically constant population of insects, but an eventually nonexistent human population (See Figure 3). When there is a small α and a small β , the insect populations will be constant again and the human population still decreases to zero eventually but at a more gradual pace (See Figure 4). If there is a big α and a big β , it is very similar to having a big α and a small β . The insect populations are fairly constant and the human populations will go to zero (See Figure 5). With a small α and a big β , it is very similar to having a small α and a small β with the human population decreasing gradually to zero(See Figure 6). As one would guess, with an α and a β in the middle of the ranges, the human population still decreases to zero but at a rate that is more gradual than in Figure 3 but quicker than what is happening in Figure 4 (See Figure 7).

Initial conditions were set to reflect reported proportions of infections. The percentage of infected bugs is approximately 30 % [6] so, S_b is set initially to 800 and I_b is set to 200. The percentage of infected people is approximately 44 % [6] so, S_p is set initially to 600, $I_{pa} = 0$, $I_{pl} = 350$, and $I_{pc} = 50$. The solutions were obtained over a period of 10000 weeks which is just under 20 years.

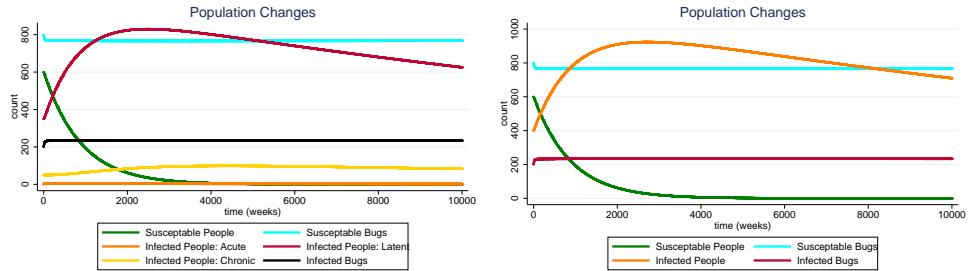


Figure 3: population dynamics with $\alpha_{aa}=0.000005$ $\alpha_{al}=0.125$ $\alpha_{ac}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.0000005$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{ap}=0.0003$ $\delta_{ab}=0.05$ $\mu_p=0.000325$ $\mu_b=0.05$ $\theta=0.015$. big alpha, small beta

Therefore, appropriate values for α_a , β_c , and θ are needed. All other parameters are definite in their values. By inspection of the eigenvalues of the Jacobian at differing values of α and β , it was found that $\alpha_a = 0 - 0.0000005$ and $\beta_c = 0 - 0.00005$ produce real eigenvalues of which 5 are negative and 1 is positive(For every selection of parameters, there was always one positive eigenvalue). These parameter values were investigated using the stochastic model(See Figure 8.

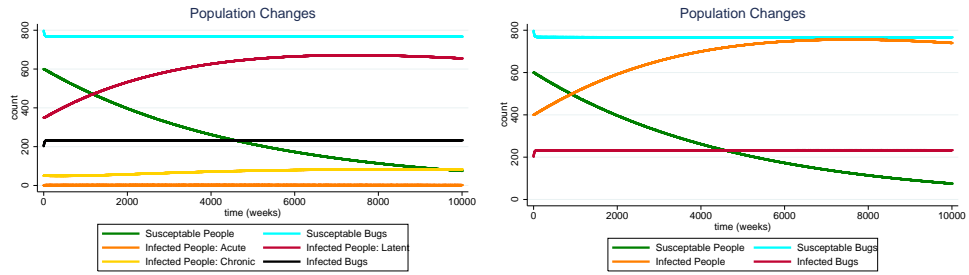


Figure 4: population dynamics with $\alpha_{aa}=0.000001$ $\alpha=0.125$ $\alpha_{ac}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.0000005$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{ap}=0.0003$ $\delta_{ab}=0.05$ $\mu_p=0.000325$ $\mu_b=0.05$ $\theta=0.015$. small alpha, small beta

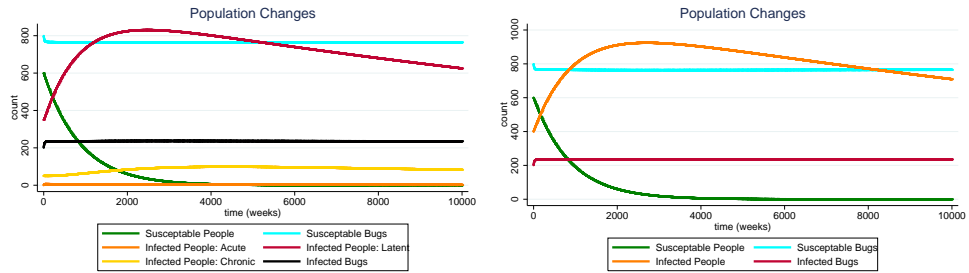


Figure 5: population dynamics with $\alpha_{aa}=0.000005$ $\alpha=0.125$ $\alpha_{ac}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.0000001$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{ap}=0.0003$ $\delta_{ab}=0.05$ $\mu_p=0.000325$ $\mu_b=0.05$ $\theta=0.015$. big alpha, big beta

There were 13 different events: 3 birth, 4 death, and 6 transition events. By visual inspection of the boxplots of population counts after 10000 weeks, the parameters $\alpha_a=0.0000001$, $\beta_c=0.00001$, and $\theta=0.015$ were found to give average proportion of infecteds close to the values observed by Breniere [6].

Figure 9 shows the solution to the ODE with these parameter values.

Figures 10, 11, and 12 show the results of the sensitivity analysis which confirms that any other selection of the parameters would give you values that are farther away from values you wish to obtain.

4 Conclusion

In this paper, a deterministic and stochastic models were developed inspired by the model of Devillers [4]. Their parameter values, however, were not appropriate for our model and thus did not lead to realistic levels of infection in either the human or insect populations. On the other hand, Devillers inclusion of the reservoir was crucial in maintaining a particular level of infection in the insect population. Through the analysis of the ODE model, it was determined that there was an unstable equilibrium point which means that any introduction of infection

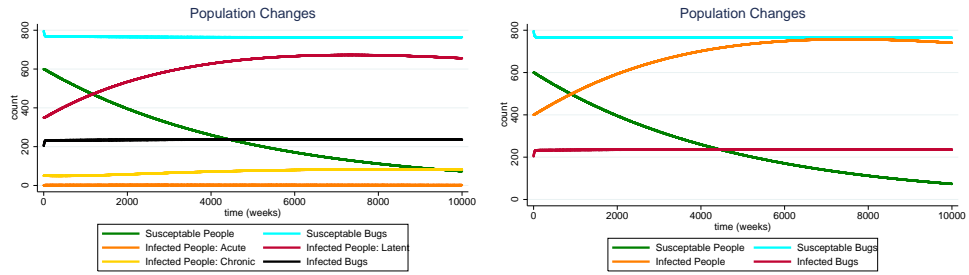


Figure 6: population dynamics with $\alpha_{aa}=0.000001$ $\alpha=0.125$ $\alpha_{ac}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.000001$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{tap}=0.0003$ $\delta_{tab}=0.05$ $\mu_p=0.000325$ $\mu_b=0.05$ $\theta=0.015$. small alpha, big beta

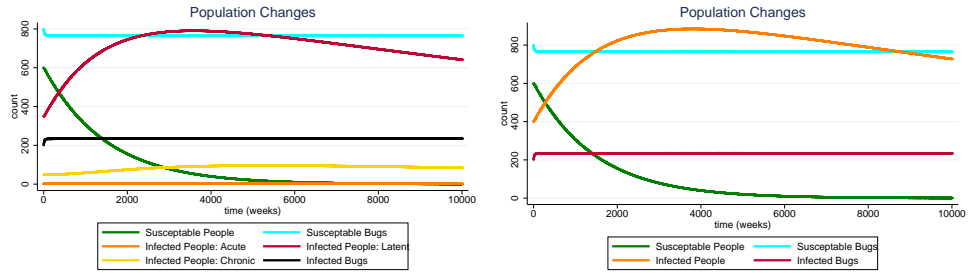


Figure 7: population dynamics with $\alpha_{aa}=0.000003$ $\alpha=0.125$ $\alpha_{ac}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.0000008$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{tap}=0.0003$ $\delta_{tab}=0.05$ $\mu_p=0.000325$ $\mu_b=0.05$ $\theta=0.015$. medium alpha, medium beta

will lead to a significant proportion of the human population infected. This highlights the necessity of exterminating the *Triatoma sp.* insects near human habitation since the removal of the disease reservoir in small mammals is impossible. This paper represents a significant addition to the literature on the mathematical modeling of Chagas disease because it enabled a more accurate estimation of rates of infections for humans and insects.

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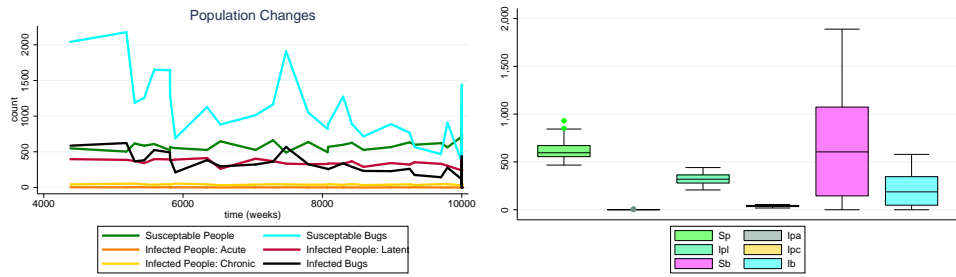


Figure 8: population dynamics with $\alpha_{aa}=0.0000001$ $\alpha_{al}=0.125$ $\alpha_{phc}=0.0001$ $\beta_{aa}=\beta_{ac}/4$ $\beta_{al}=\beta_{ac}/2$ $\beta_{ac}=0.00001$ $\gamma_{aa}=0.00003$ $\gamma_{al}=0.00001$ $\gamma_{ac}=0.0005$ $\delta_{tap}=0.0003$ $\delta_{tab}=0.05$ $\mu_{p}=0.000325$ $\mu_{b}=0.05$ $\theta=0.015$.

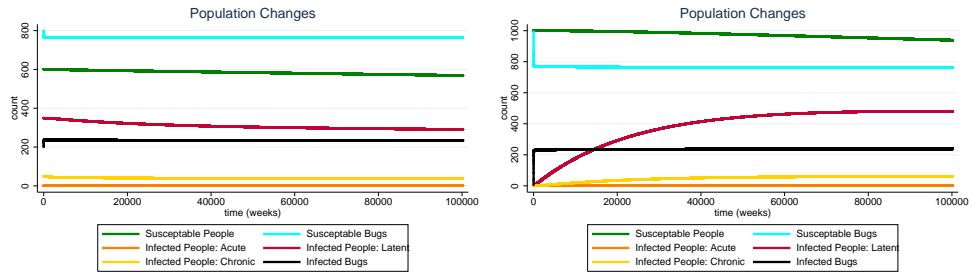


Figure 9: Left:Results of the new parameter values with the initial populations set to $S_p=600$, $S_b=800$, $I_{pa}=0$, $I_{pl}=350$, $I_{pc}=50$, and $I_b=200$. Right:Results of the new parameter values with the initial populations set to a disease free state of S_p and $S_b=1000$ and I_{pa} , I_{pl} and $I_{pc}=0$

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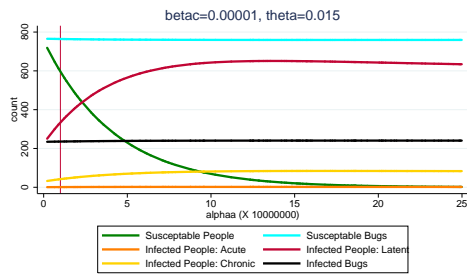


Figure 10: Analysis of α_a while β and θ are 0.00001 and 0.015, respectively

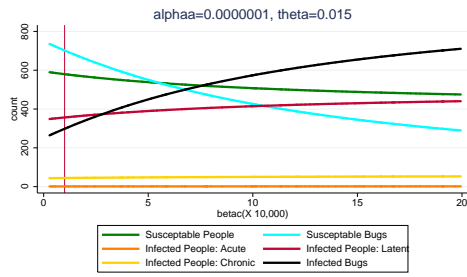


Figure 11: Analysis of β_c while α and θ are 0.0000001 and 0.015, respectively

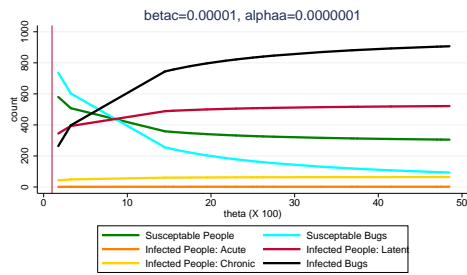


Figure 12: Analysis of θ while α and β are 0.0000001 and 0.015, respectively