

Getting Down on Dengue

New Mexico
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Executive Summary

This project aims to create a realistic model of the spread of Dengue Fever in Cuba. Through applying both a traditional system dynamics approach and a novel agent-based model approach, we were able to understand the disease from two unique perspectives. Docking these two approaches allowed us to further investigate the spread of dengue fever as well as the benefits and properties of each respective method. For our system dynamics model we used a vector-based modification of the time-honored SIR differential equations implemented in the NetLogo System Dynamics Modeler. For our agent-based model, we implemented the NetLogo GIS Extension to create a multilayered model of Cuba that includes elevation, rainfall, and population density. Through modeling the collection of rainwater, we were able to estimate the mosquito population and, in turn, the spread of the disease in Cuba. With the Behavior Space tool in NetLogo, we were able to explore the sensitivity of parameters in both models as well as dock them against one another. By comparing both our system dynamics model and our agent-based model against real world data, we proved the importance of small-scale source reduction (water removal) in deterring mosquitoes and hindering the spread of Dengue Fever in Cuba.

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Introduction and Epidemiology

Dengue Fever, dubbed “breakbone fever” by United States Founding Father Benjamin Rush, is one of the most prevalent and destructive tropical diseases in today’s world. It is the most common viral disease transmitted by arthropods (arbovirus) and is endemic in over 100 countries, with an estimated 2.5 billion people currently at risk of infection. In the wake of the Second World War, countries in South America and Southeast Asia were the first to experience epidemics of Dengue Fever and it is now a severe problem in these tropical countries due to urbanization and population growth. Research done by the World Health Organization (WHO) estimates that about 50 million cases of Dengue Fever occur in the world every year and that this number is increasing exponentially. For example, in 2001, there were 400,000 reported cases of Dengue Fever in all of Southeast Asia, whereas, in Rio de Janeiro alone, there were 500,000 cases in 2002. Furthermore, in response to climate change, Dengue Fever is now spreading further north, with cases being reported in Florida and Texas this past decade.

Dengue Fever is a mosquito-borne viral disease that can be caused by four distinct serotypes (known as DENV-1, DENV-2, DENV-3, and DENV-4). The existence of these four distinct strains has made the development of a vaccine for the virus unachievable. Infection with one of the serotypes usually results in lifelong immunity to that serotype (homologous immunity) but only temporary immunity to the other strains (heterologous immunity), allowing for complications to develop upon secondary infection. The symptoms of Dengue Fever (DF) include sudden

fever, severe headache, muscle/joint pain, and the development of a characteristic skin rash (islands of white in a sea of red). These symptoms usually appear four to seven days after infection (incubation period) and can last anywhere from three to ten days. While 80% of Dengue Fever cases are mildly symptomatic or completely asymptomatic, the disease can also develop into two other life-threatening forms: Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Dengue Hemorrhagic Fever is characterized by the same external symptoms as classic DF, however, the leakage of plasma from blood vessels, resulting in internal bleeding and loss of circulation, is what makes DHF far more lethal. Studies have proven that those who have previously been infected with DF are far more likely to develop DHF.

The vectors of the Dengue Fever virus are mosquitoes of the genus *Aedes* and, most commonly, of the species *aegypti*. The *Aedes aegypti* mosquito, commonly called the “yellow fever mosquito”, is highly anthropophilic, inhabiting densely populated urban areas where it has easy access to human blood-meals, which are required for the mosquito to reproduce. If a female mosquito bites a human infected with Dengue Fever, the virus becomes present in its salivary glands within eight to ten days and that mosquito becomes infected for the rest of its life. After biting a human and mating, female mosquitoes require standing water in order to undergo oviposition. The removal of breeding sites for female mosquitoes, known as “source reduction”, is one of the major control methods being implemented in countries that suffer from Dengue Fever. As opposed to the use of toxic insecticides, source reduction provides an efficient and effective way to control the spread of Dengue

Fever that requires self-initiative of citizens in places where *Aedes aegypti* run rampant.

Our models focus on the spread of Dengue Fever in the island nation of Cuba, which currently ranks fifth for concentration of DF and DHF cases in Latin America. We have chosen Cuba as our location because it is geographically isolated, exhibits the perfect year-round climate for the breeding of *Aedes aegypti* mosquitoes, and has a history of devastating Dengue Fever epidemics. Starting with DEN-1 in 1977 and later DEN-2 in 1981, both Dengue Fever and Dengue Hemorrhagic Fever have had a severe impact on the population in Cuba. More recently, over 11,000 people became infected with Dengue Fever in 2002, resulting in a fatality rate of 8.3%. By comparing our models against real-world data, we hope to identify and quantify the efficacy of small-scale source reduction in hindering the spread of Dengue Fever. Our analysis shows that simply by emptying a rain-barrel or draining an empty tire, Cubans have the power to help prevent Dengue Fever in their community and their country.

System Dynamics

Derivation

Since the work of Kermack and McKendrick in 1927, deterministic compartmental models have been the traditional approach to computational epidemiology. These types of models use a set of ordinary differential equations to describe the evolution of a disease through various compartments of a population. Most basically, three equations can be used to describe the relative number of people susceptible to a disease (S), infected by a disease (I) and recovered from a disease (R) over time, as follows:

$$\begin{aligned}dS/dt &= -\beta SI \\dI/dt &= \beta SI - \gamma I \\dR/dt &= \gamma I\end{aligned}$$

where β is the contact rate between the susceptible compartment and the infected compartment and γ is the recovery rate from the disease.

However, the above equations are only suitable for a model in which the total population remains constant. In order to imitate the spread of a disease over longer time-scales, where the rates of infection and recovery are as important as the rates of natural birth and death, we must modify our equations:

$$\begin{aligned}dS/dt &= hS - \beta SI - \mu S \\dI/dt &= \beta SI - (\gamma + \mu + \delta)I \\dR/dt &= \gamma I - \mu R\end{aligned}$$

with h representing the birth rate of susceptible, μ representing the natural death rate, and δ representing the death rate due to the infection.

Furthermore, both models presented above are only applicable to infections spread by human-to-human contact. In order to model the transmission of Dengue Fever between the *Aedes aegypti* mosquito and infected humans, we must modify our set of differential equations to include two vectorial compartments:

$$\begin{aligned}dS/dt &= hS - \beta SI_V - \mu S \\dI/dt &= \beta SI_V - (\gamma + \mu + \delta)I \\dR/dt &= \gamma I - \mu R \\dS_V/dt &= qS_V - \alpha S_V I - eS_V \\dI_V/dt &= \alpha S_V I - eI_V\end{aligned}$$

where q now represents the birth rate of susceptible vectors (S_V), α represents the contact rate between susceptible vectors and infected humans, and e represents the natural death rate of the vector population.

Notice that, in this final set of five equations, there are two separate infection rates, one for vectors and one for humans. This is due to the fact that the infected vector compartment (I_V) determines the derivative of infected humans (I) while the infected human compartment (I) determines the derivative of infected vectors (I_V). These infection rates allow us to calculate the most important parameter in the transmission of an infection, the reproductive number or R_0 . The value of R_0 determines the number of secondary infections caused by an infected person during

the duration of their infection. This, in turn, determines whether or not an epidemic will occur for a given disease in a given population. If R_0 is greater than unity, the disease will be detrimental to the population, while if R_0 is less than unity, the disease will simply die out. In the case of Dengue Fever the basic reproduction number can be calculated as follows:

$$R_0 = (\alpha + \beta)(S + I + R)/\gamma$$

For our model of Dengue Fever, the values of the respective infection rates are derived from the biting rates of *Aedes aegypti* mosquitoes and the probability of human-vector transmission as employed by Derouich, Boutayeb, and Twizell. Lastly, observe that the set of equations we have derived for our model of Dengue Fever only considers one strain of the virus. For the sake of computational ease and effective comparison with our Agent Based Model, we have chosen to limit the scope of our models to the spread of the DEN-1 serotype.

Implementation

In order to computationally implement our SIR + V epidemiological equations we used the NetLogo System Dynamics Modeler. In the System Dynamics Modeler, the equations are visualized as a diagram of stocks and flows in which stocks represent the respective compartments of the population and flows represent the differential equations that govern those compartments. Variables such as birth and death rates are depicted as diamonds that are connected to the flows by links. These variables can be controlled by sliders in the NetLogo interface, where

the values of respective compartments can be plotted over time to monitor the spread of the infection.

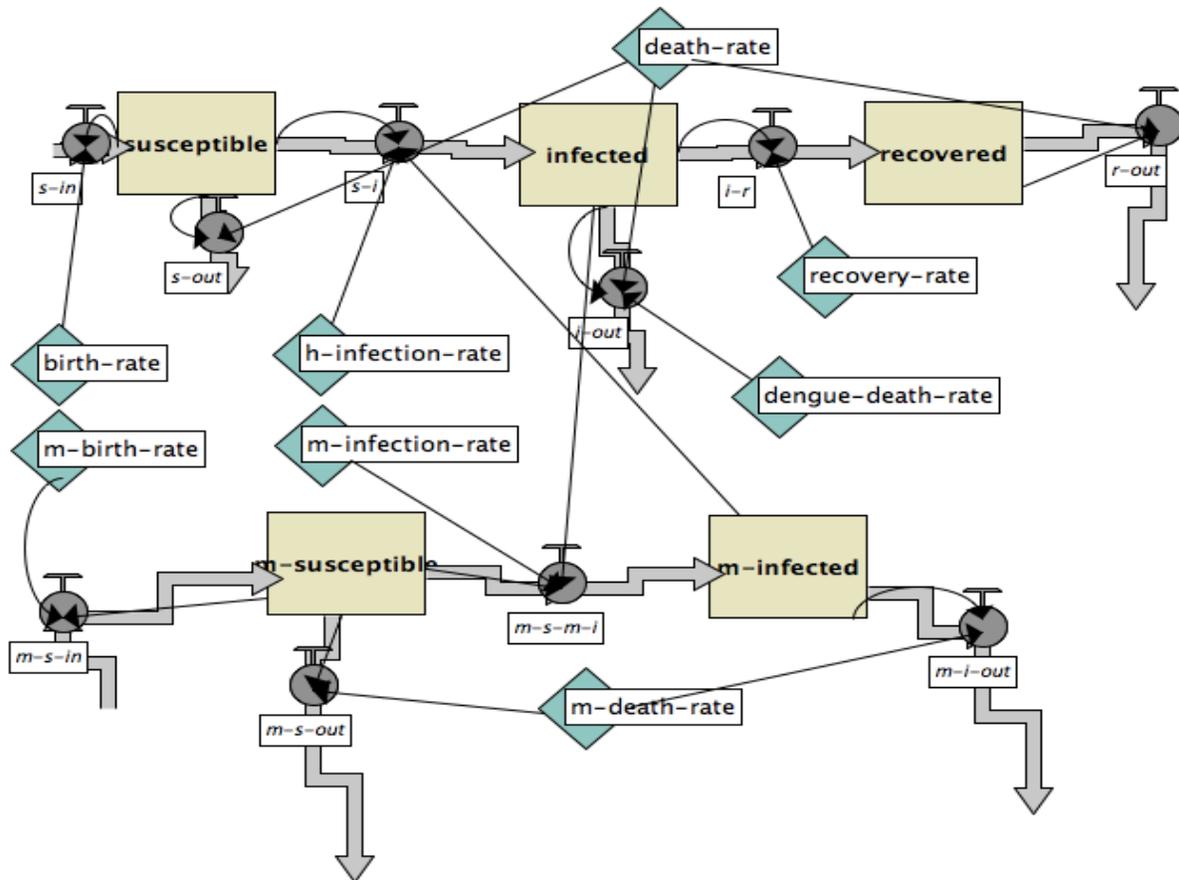


Figure 1: Stocks and flows of NetLogo System Dynamics Modeler. Using parameter values from our Agent-Based Model, we were able to

simulate the spread of Dengue Fever in Cuba over varying time periods. The human birth and death rates were calculated based on the inverse of the human life span (~70 years) multiplied by the crude birth (11.2) and death rates (7.9) from the 2012 Cuban census. Similarly, the mosquito birth and death rates are the inverse of the average mosquito lifespan (~25 days). The recovery rate is simply the inverse of the average duration of the infection (~15 days).

Parameter Values for System Dynamics Model

Human Birth Rate	h	.000448 (daily)
Human Death Rate	μ	.000316 (daily)
Recovery Rate	γ	.067 (daily)
Human Infection Rate	β	$.75/(S + I + R)$
Mosquito Infection Rate	α	$.375/(S + I + R)$
Dengue Death Rate	δ	.05
Mosquito Birth Rate	q	.04 (daily)
Mosquito Death Rate	e	.04 (daily)
Human Population	$S + I + R$	632,900
Mosquito Population	$S_V + I_V$	15,120
Initial Mosquitoes Infected	Variable	50%

For these values of the parameters, we set the “dt” of the System Dynamics Modeler to unity, which correlates to one time-step (tick) per day. When we run the model for 180 days, we get the following graph of the human and mosquito populations

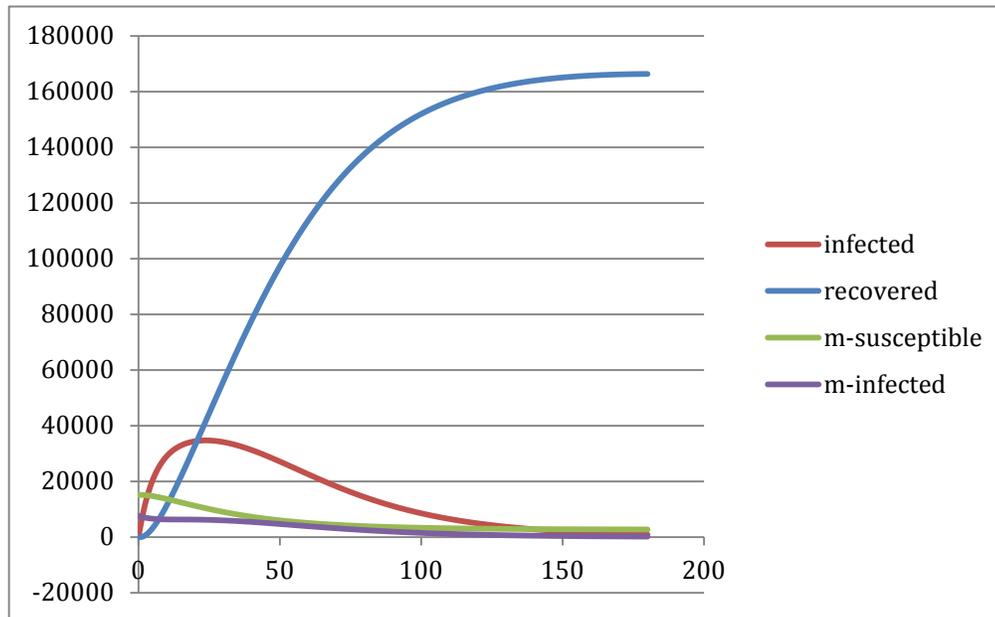


Figure 2: Infected humans, recovered humans, susceptible mosquitoes and infected mosquitoes (y axis, population) plotted as a function of time (x axis, days).

From this curve we can see that an epidemic does occur for the aforementioned parameter values ($R_0 = 4.2$). The peak of this epidemic happens 24 days into the model and affects 34,700 humans (5.5% of population), followed by a corresponding rise in the recovered population. Using the NetLogo Behavior Space tool we can see how the severity and timing of the epidemic are dependent upon the percentage of mosquitoes that are initially infected.

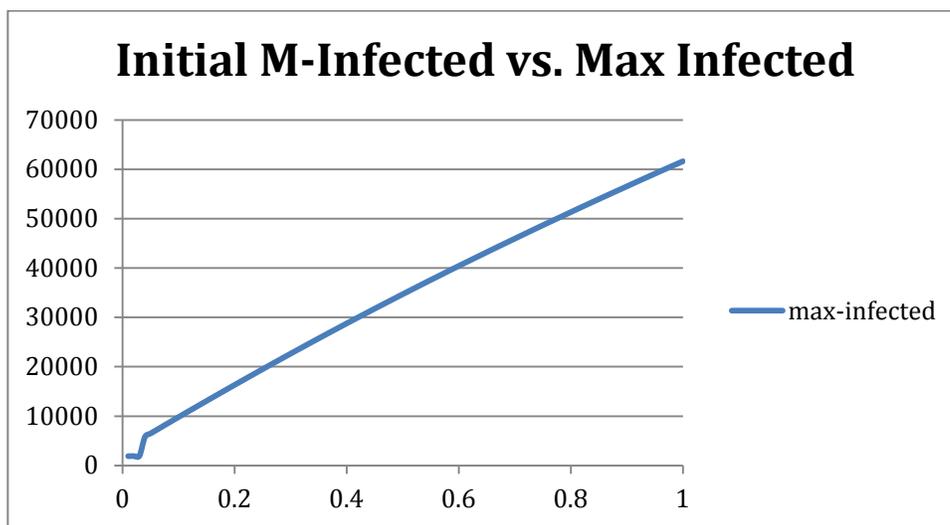


Figure 3: Maximum number of infected humans (y axis) as a function of the initial percentage of infected mosquitoes (x axis).

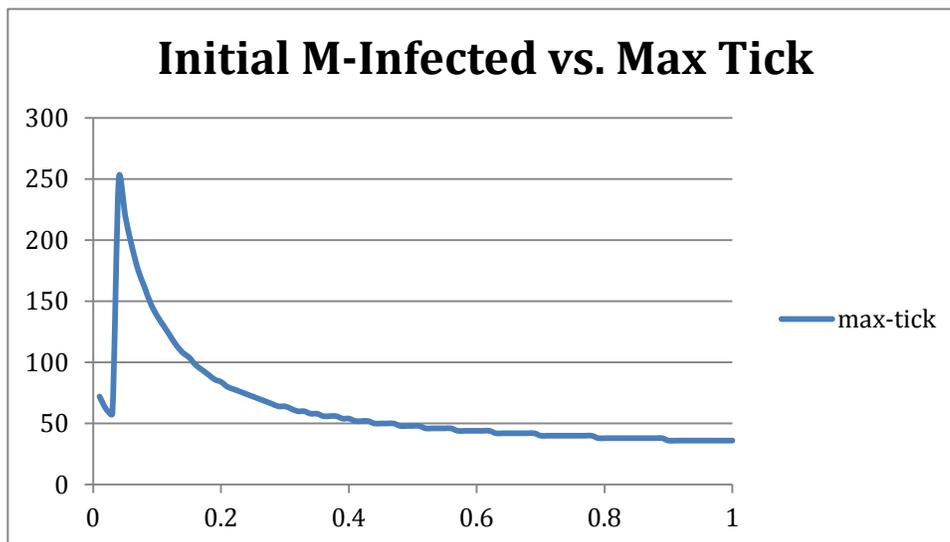


Figure 4: Day at which human infection peaks (y axis) as a function of the initial percentage of infected mosquitoes (x axis).

For values greater than .1, there is clearly an almost linear relationship between the magnitude of an epidemic and the percentage of mosquitoes that are initially infected. Furthermore, as the percentage of initially infected mosquitoes rises, the peak of the epidemic occurs sooner in the model, implying that disease spread faster. This behavior is an example of the macro-level insight that System Dynamics models provide.

Agent Based Model

In order to better understand the micro-level behavior of our model, we also created a multilayered Agent Based Model of the spread of Dengue Fever in Cuba. The bottom layer of this simulation is the GIS (Geographic Information System) layer, which imports real-world data into NetLogo through the NetLogo GIS Extension. By obtaining and mapping GIS files for elevation, surface water, and population density in Cuba we were able to monitor how the accumulation of rainfall affected the spread of Dengue Fever in major urban areas.

Water Layer (Elevation/Rainfall)

The first GIS dataset we considered was that of elevation. By knowing the elevation at every point throughout Cuba, we could model where standing water would collect and allow mosquitoes to breed. When we combined our GIS elevation data with monthly rainfall data, we were able to successfully imitate the large-scale accumulation of rainwater.

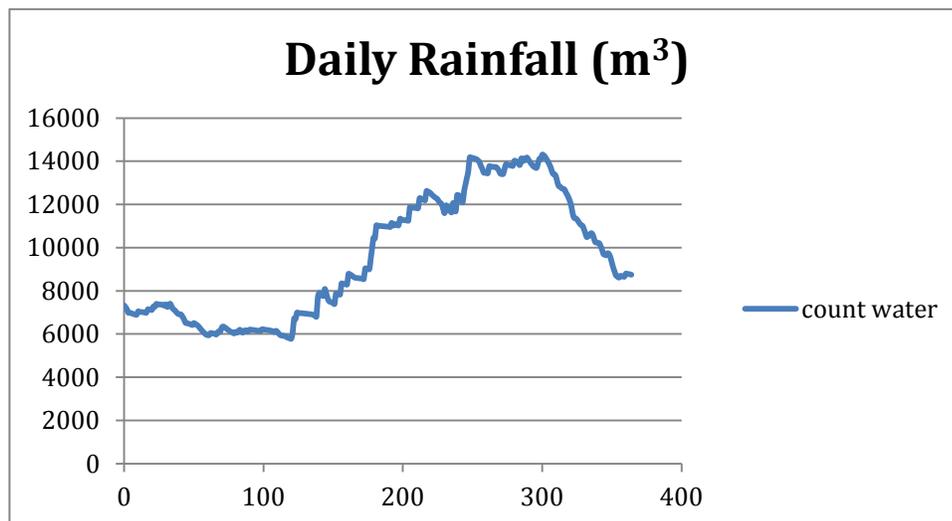


Figure 5: Daily rainfall accumulation (m³) over the period of a year.

When modeling the rainfall, we simulated the random emergence of storms at different points across the island. These rainstorms release the entirety of their water agents onto one point and the agents move according to the elevation of the patches below them. We also assume that 40% of the water is initially lost to infiltration (absorption by soil) and that subsequent amounts are lost to evapotranspiration, which also varies monthly. Finally, we also imported GIS data for existing surface water in Cuba to consider all possible sites for mosquito oviposition.

Agent Layer (Humans/Mosquitoes)

Not only is Dengue Fever transmission dependent on mosquito-human interaction, but mosquito oviposition also requires a human blood meal. This implies that the human and mosquito populations cannot be autonomously modeled, but are computationally codependent.

Based on GIS data for human population density in Cuba, we are able to approximate one hundred humans for each agent. We then use the crude birth and death rates from the 2012 Cuban census to model the gradual growth of the human population. Furthermore, we assume a human lifespan of 25,000 days or about 70 years (as in the System Dynamics Model).

The mosquito population is more difficult to model, as it is dependent on the presence of humans and water. Logically, we have chosen to only model female

mosquitoes, as they are the gender that spreads the disease and reproduces, and we assume a 50/50 sex ratio for mosquitoes. We approximate the lifespan of the adult mosquito to be 25 days and assume that the period of development from egg through pupa takes approximately 12 days.

A series of rules can be compiled to govern the life cycle and oviposition of the mosquitoes. When a mosquito is born, it is seeking a blood meal, and therefore sets its heading towards the nearest human. After that mosquito has been fed, it sets its heading towards the nearest water in order to deposit eggs and spawn 37 more mosquitoes. Based on experimental evidence, we limit the number of times a mosquito can reproduce to six.

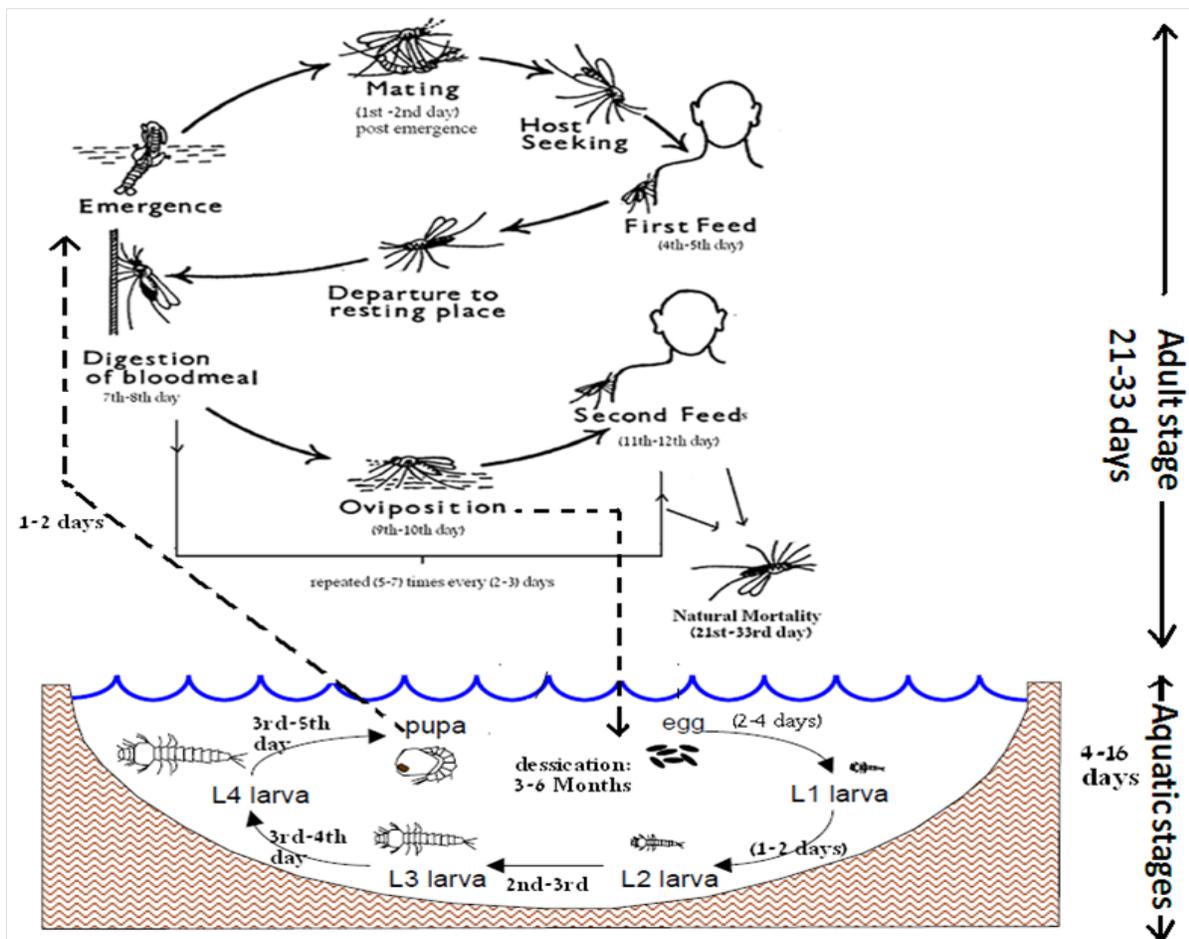


Figure 6: Mosquito lifecycle with timescales (Elthahir Group at MIT).

Phase Space Analysis

Using the Behavior Space tool in NetLogo we were able to test the sensitivity of the model to various parameters. To begin, we analyzed how variance in the biting rate, or probability that a hungry mosquito will bite a human on the same patch, affected the severity of the epidemic.

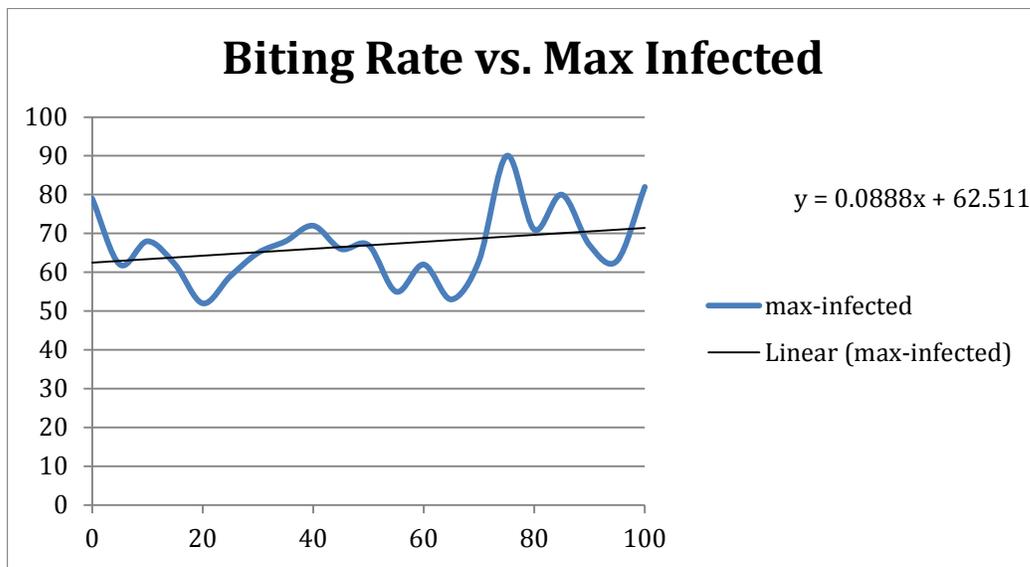


Figure 7: Maximum number of infected humans (y axis) as a function of percentage human biting probability (x axis).

Because the biting rate is not directly related to the transmission of the infection within the Agent Based Model, there is no obvious increase in the severity of the epidemic. However, the biting rate does allow for the mosquito population to increase more effectively and, in turn, infect more humans, resulting in an overall positive slope in the graph above.

Next, we investigated how the infection rate parameter played a role in amplifying the epidemic. The infection rate acts as the probability that an agent (mosquito or human) will become infected if it is on the same patch as an infected agent. This parameter should have a direct effect on the severity of the spread of the disease.

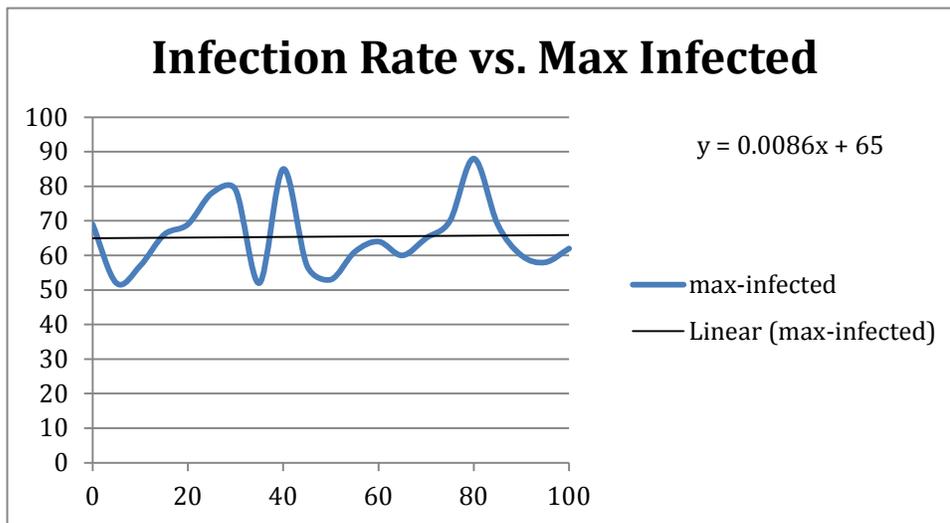


Figure 8: Maximum number of infected humans (y axis) as a function of infection rate (probability, x axis).

Surprisingly, as can be inferred from the graph above, the infection rate has very little influence on the severity of the infection.

Thirdly, we analyze the parameter of the mosquito velocity or flight range.

According to the World Health Organization (WHO), the flight range of an *Aedes aegypti* mosquito is usually only 400 meters throughout its lifetime (25 days).

Experiments done in Thailand over a ten-day period found that *Aedes aegypti* traveled, on average, 85 meters away from their hatchsite. By converting these two flight ranges to velocities and averaging them together, we estimate that the

mosquito velocity is approximately 12.25 meters per day. In our NetLogo world, the width of a single patch is about 8.66 km (each patch is 75 square kilometers), allowing us to convert our mosquito velocity to .0014155 patches per day. When we allow the model to run with this naturally calculated mosquito velocity, we find that the mosquito population always dies out within the first two months of the simulation. However, when we raise the mosquito velocity to a reasonable rate, we find that the mosquito population explodes exponentially. We used the Behavior Space tool in NetLogo to find the mosquito velocity value that provides a steady mosquito population.

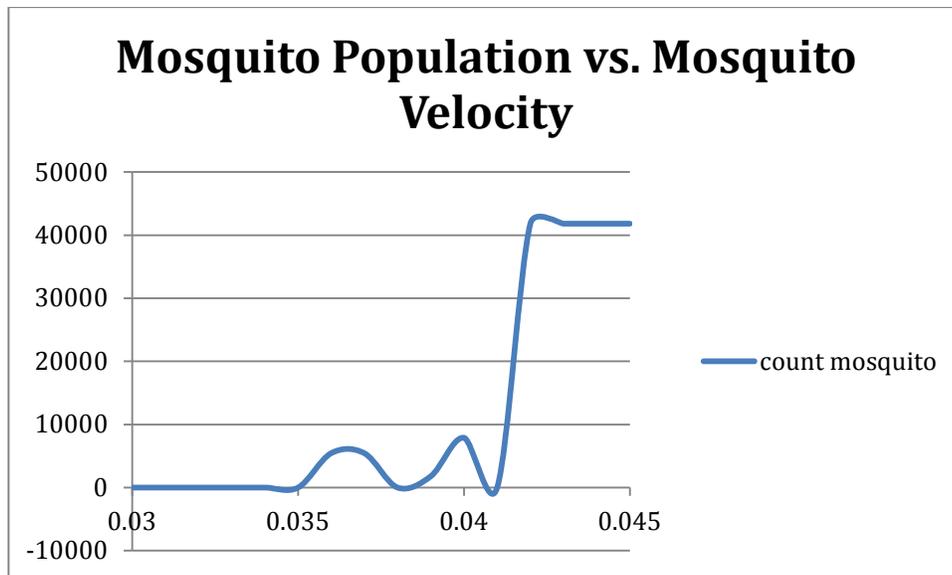


Figure 9: Mosquito populations after 60 days (y axis) as a function of mosquito velocity in patches per day (x axis).

Through analysis of the graph above, the equilibrium value for the mosquito velocity sits at around .04 patches per day. This value corresponds to .3464 kilometers per day or a flight range of approximately 8.66 kilometers. Remember that 8.66 km is also the length of a single patch in our NetLogo world, implying that this mosquito

velocity allows a mosquito to move approximately one patch in its lifespan. With the natural velocity of .0014155, mosquitoes do not have enough time to explore other patches in search of human blood meals or standing water.

Lastly, we experimented with the most obviously influential parameter in our Agent Based Model: the initial percentage of infected mosquitoes, or “initial infected rate”. The model naturally breeds exactly 1512 mosquito agents (which each represent 10 actual mosquitoes) at the start of each model based on GIS surface water data for Cuba. The percentage of these mosquitoes that are infected at the start of the model is determined by the initial infected rate.

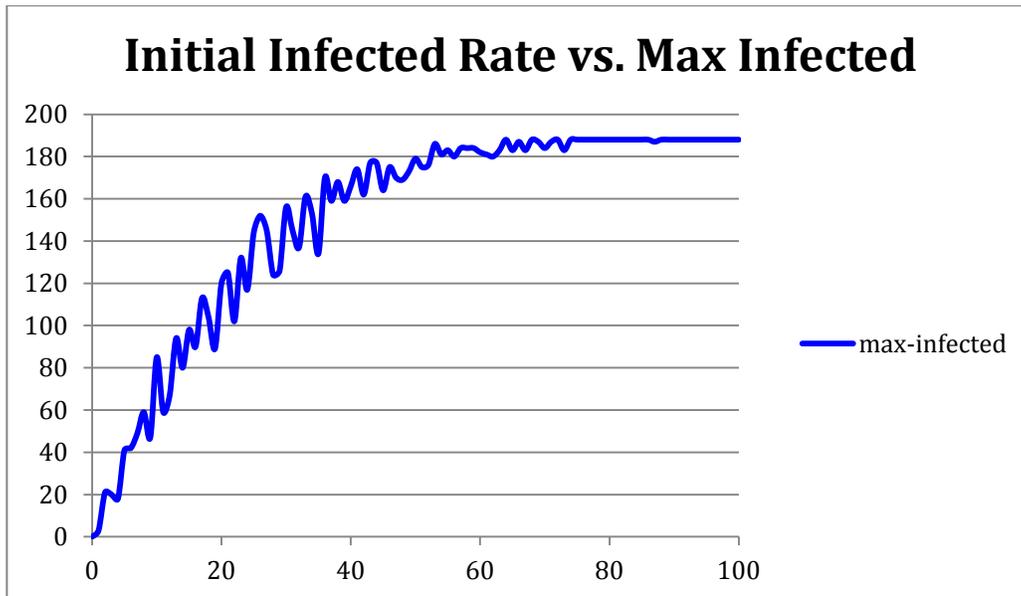


Figure 10: Maximum number of infected humans (y axis) as a function of the initial percentage of infected mosquitoes (x axis).

As you can tell from the graph, increasing the percentage of mosquitoes that are initially infected increases the maximum number of humans infected in the epidemic. This increase is greatest at low initial mosquito infection with a slope of 5

infected humans/% infected mosquitoes until about 20% initially infected mosquitoes. Above 20% initial mosquito infection rate the response of human infections to it drops first and then saturates, which limits the maximum number of infected humans at 188. This saturation implies that only approximately 65% percent of the initial population of mosquitoes has to be infected in order to produce the most severe epidemic.

Discussion and Solutions

Comparison of Approaches

By modeling the spread of Dengue Fever using both System Dynamics and Agent Based approaches, we were able to explore the sensitivity of more parameters as well as compare the two models. We found that the System Dynamics Model gave us a more analytical approach to modeling the disease that provided a better understanding of the macro-level behavior of an epidemic. On the other hand, our Agent Based Model allowed us to take a more numerical approach to comprehending Dengue Fever and was best for considering how the micro-level behavior of individual agents affects the overall epidemic. Furthermore, the Agent Based Model allowed us to test the sensitivity of far more parameters than the System Dynamics Model. One parameter sweep that both models shared was that of the initial percentage of infected mosquitoes.

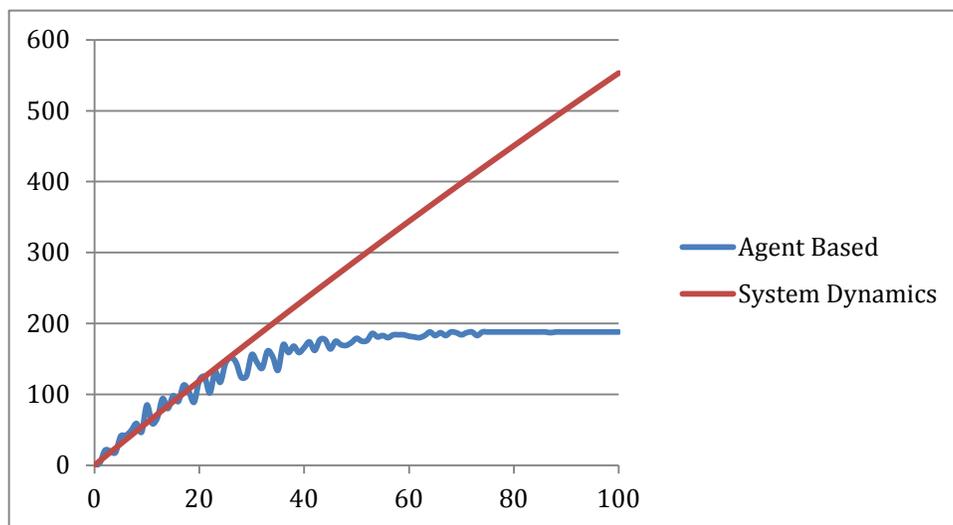


Figure 11: Comparison of maximum number of infected humans as a function of initial percentage of infected mosquitoes in Agent Based and System Dynamics. Raising initial mosquito infection rates at low values (below 20%) increases the

maximum infected humans in a linear and similar manner in both models. However, the micro-level behavior of the Agent Based Model becomes apparent in the saturation of this parameter sweep. While the epidemic size in the System Dynamics model continues to grow almost linearly with the initial percentage of infected mosquitoes, the Agent Based Model levels off, most likely due to the global resolution of the model.

When we compare both models against real-world epidemics in Cuba, we find that, while Dengue outbreaks commonly occur within a year, there are also longer trends of the disease that our model does not replicate. These large-scale trends are probably more dependent on properties in the mosquito population dynamics that vary based on yearly rainfall and temperature as well as random arrival of infection in the human population through international travel.

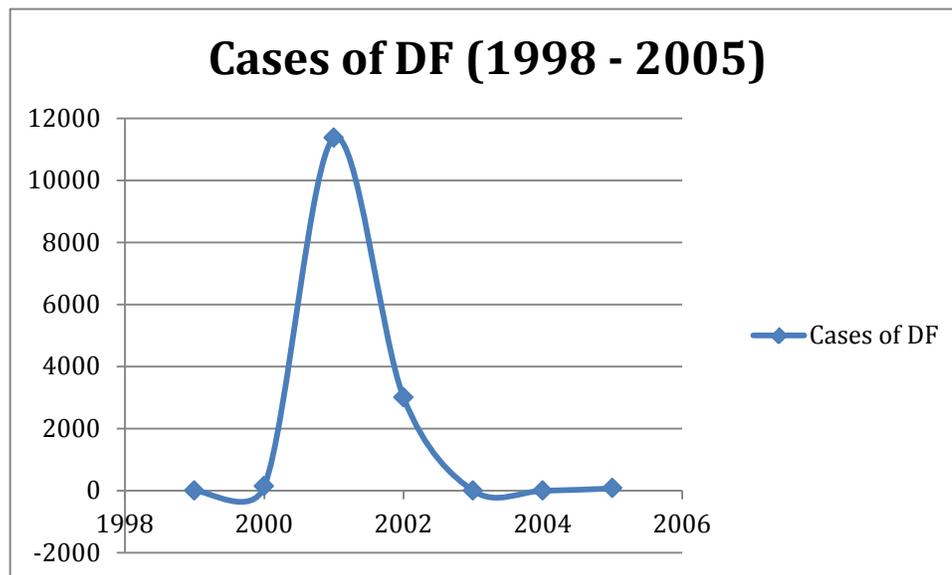


Figure 12: Real-world values for the number of Dengue Fever cases in Cuba between 1998 and 2005
Using our Agent Based Model we were able to simulate various control

strategies for the spread of Dengue Fever including the limitation of human mobility, the development of a vaccine, and the implementation of source reduction.

Human Mobility

The first control strategy for the spread of Dengue Fever that we considered is the limitation of human mobility. Limiting the influx of people into various provinces reduces the probability that Dengue Fever will spread to that province. In our Agent Based Model we controlled two parameters regarding the limitation of human

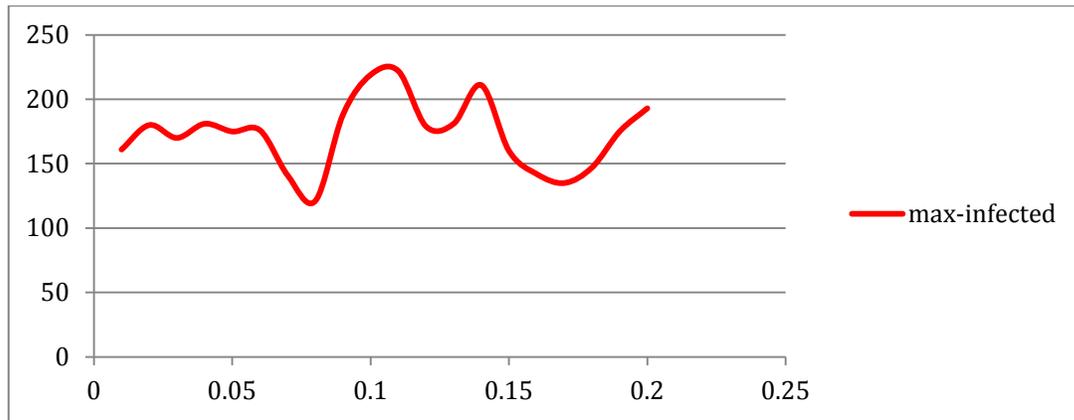


Figure 13: Maximum number of infected humans as a function of range of mobility

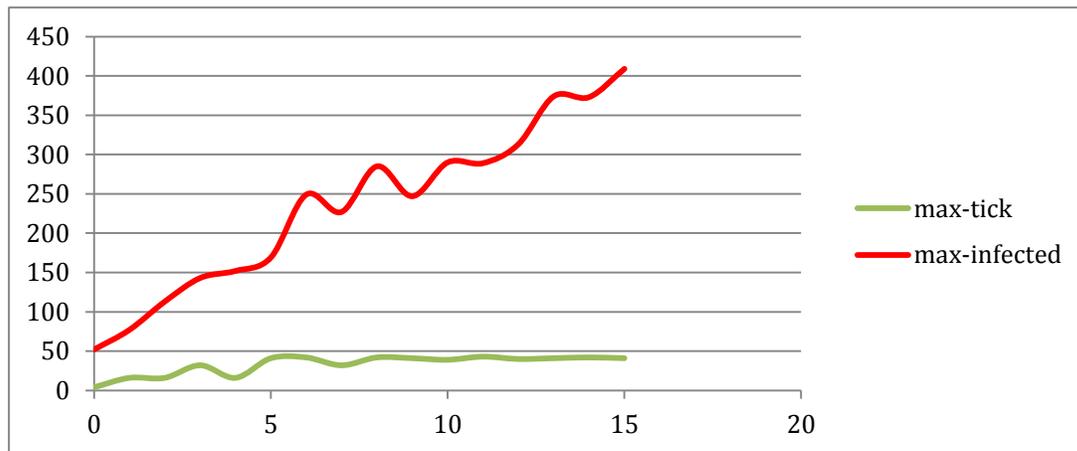


Figure 14: Maximum number of infected humans and day of peak infection as a function of the percentage of the population that is mobile

mobility: the radius of mobility and the percentage of the population that is mobile. As you can tell from the graphs, the range of human mobility has little effect on the severity of the epidemic. However, the percentage of the population that is mobilized has a direct effect on both the magnitude and the speed of the epidemic. Therefore, limiting human mobility is not necessarily an effective strategy for controlling Dengue Fever (see Appendix).

Vaccination

Currently there is no vaccine available for any of the four serotypes of Dengue Fever. Using our Agent Based Model we were able to predict the effectiveness of a vaccine in reducing the spread of a single strain of Dengue Fever.

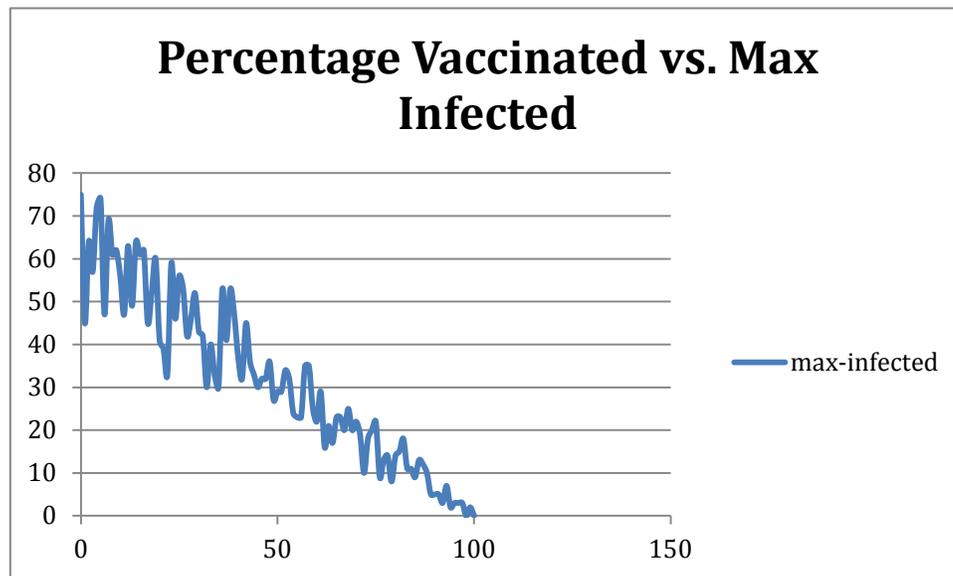


Figure 13: Maximum number of infected humans as a function of initial percentage of humans vaccinated
Obviously, the presence of vaccinated population has a beneficial effect on limiting

the spread of the disease. While there is still large variance in epidemic size due to other parameters, vaccination is a very useful control strategy.

Source Reduction

The final control strategy we considered using our Agent Based model is that of source reduction. Source reduction is the elimination of standing water to reduce the number of breeding sites for *Aedes aegypti* mosquitoes. By allowing human agents within the model to remove water agents from their respective patches, we imitated source reduction at the resolution of our NetLogo world. We created a “source reduction parameter” that acted as the probability a human agent would remove the water from its patch each day.

Variance in the source reduction probability parameter has a direct effect on the magnitude of the epidemic and the rate at which the epidemic decays. With the source reduction parameter set to zero, three epidemics of about equal intensity occur, with a maximum number of infected of 68. However, with a 50% probability that each human will remove the water from its patch, the severity of the recurring infections is lessened (especially the third step) and the maximum number of infected is brought down to 56. When the entirety of the human population is participating in source reduction it is evident that the epidemic is not as severe and that it dies out more quickly. Nonetheless, we are still limited by the 75 square kilometer patch resolution of our NetLogo world. If we were to consider the fine-grained collection of water in, for example, empty tires and potholes, source

reduction could have a far greater impact in preventing the spread of Dengue Fever.

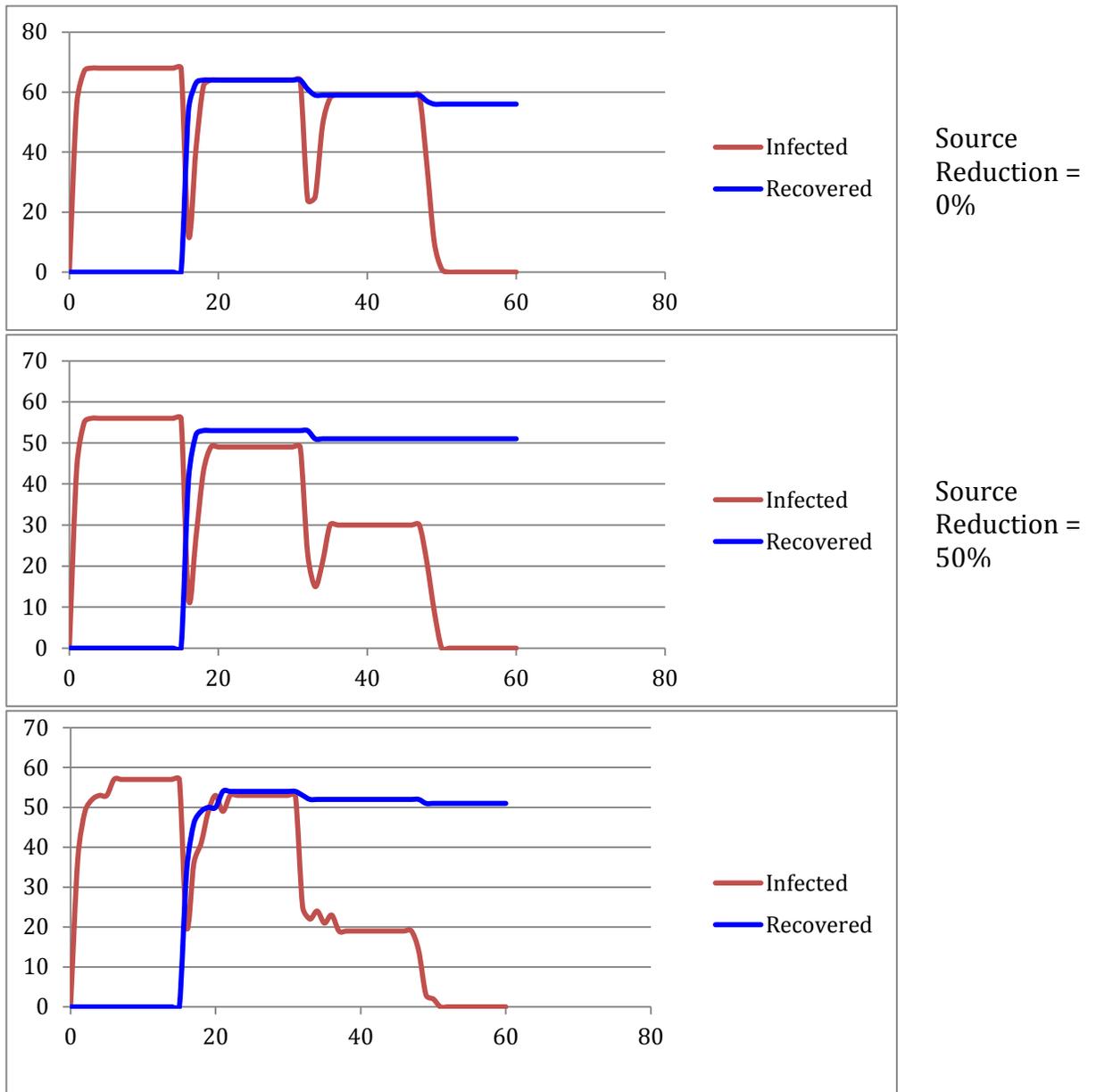


Figure 14: Total number of infected and recovered humans as a function over time over a period of 60 days with source reduction values of 0%, 50% and 100 % respectively

Conclusion

Dengue Fever is a very serious tropical illness that is currently threatening a third of the world's population and spreading to new parts of the globe each year. As this disease becomes more and more internationally destructive, preventative measures must be addressed to control the spread of infection. Through evaluating data obtained from both a System Dynamics approach and an Agent Based approach with realistic rainfall, infected mosquito life cycle and interactions with humans we make the following conclusions:

- 1) The most important parameter that influences the spread of Dengue Fever is the percentage of the mosquito population that is infected
- 2) Controlling human mobility (quarantine strategy) is not effective in preventing the spread of Dengue Fever
- 3) The development of a vaccine is a very important next step in eradicating Dengue Fever, despite difficulty of multiple serotypes
- 4) Source reduction is an easy and effective way to control the spread of Dengue Fever through the micro-level diminution of the mosquito population

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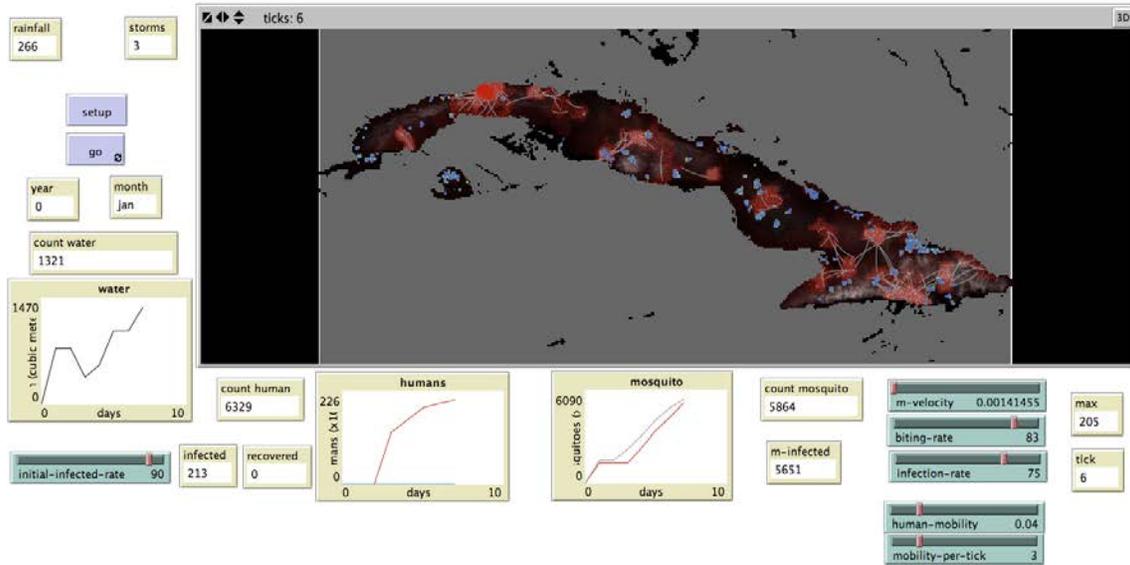
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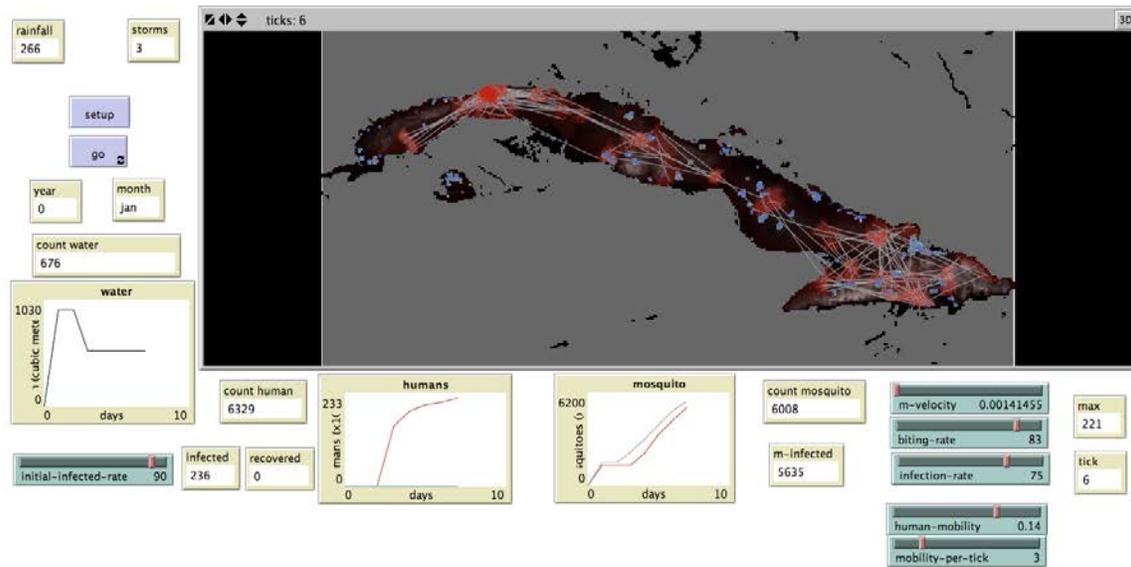
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Appendix:

Comparative screenshots of Agent Based Model with high human mobility and low human mobility, as seen through links connecting human agents.



Agent-Based Model with Low Human Mobility



Agent-Based Model with High Human Mobility