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Modeling the Spread and Prevention of Malaria in Central America

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Abstract: In 2016, the World Health Organization (WHO) estimated that there were 216 million cases of Malaria reported in 91 countries around the world. The Central American country of Honduras has a high risk of malaria exposure, especially to United States soldiers deployed in the region. This article will discuss various aspects of the disease, its spread and its treatment and the development of models of some of these aspects with differential equations. Exercises are developed which involve, respectively, exponential growth, logistics growth, systems of first-order equations and Laplace transforms. Notes for instructors are included.

1 Introduction

In 2016, the World Health Organization (WHO) estimated that there were 216 million cases of Malaria reported in 91 countries around the world. This number was five million more than that reported in 2015 [14]. More importantly, the WHO estimates that of those cases, there were 445,000 deaths reported (similar to the 446,000 from 2015). As another data point, in 2006, there were 247 million cases of malaria world-wide, causing nearly one million deaths. Approximately half of the world's population is at risk of malaria. Malaria is predominantly endemic to the tropic and subtropic regions of the globe. More than 90% of malaria cases occur on the African continent, with the remainder concentrated in parts of the Pacific, Latin America, and Asia (see Figure 1).

Inhabitants of malaria-infected countries are not the only ones at risk. Soldiers deployed to these regions are susceptible to infection. From 1995 to 2004, military clinicians reported an average of 42 cases of malaria per year in United States soldiers, with the majority of these cases developed while serving in the Republic of Korea [13]. Although this incidence rate and the epidemiological pattern have been relatively stable over the past two decades, outbreaks associated with an increase in the number of military troops deployed to malarial areas have occurred and may continue to account for an increase in malaria cases imported into the United States.

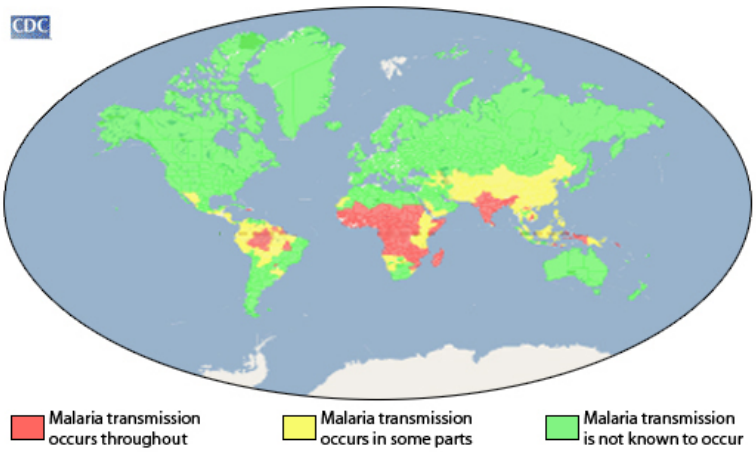

Figure 1: Malaria Map (from [8])

Most United States service members currently deployed in war zones are in Afghanistan or Iraq where malaria transmission is seasonal and varies geographically. Further, many service members have had "multiple, relatively short assignments to malaria-endemic areas" [3]. Malaria is caused by *Plasmodium* parasites, which are spread to people when an infected female Anopheles mosquito, called a malaria vector, bites the human. Believe it or not, there are more than 400 different species of the Anopheles mosquito [14], and studies show that all of the important malaria vectors bite their prey between dusk and dawn. Further, in many locations, transmission of the disease is seasonal, with peak transmission occurring during and immediately after an area's rainy season. There are five different parasite species which can cause malaria in humans [14], but two of them—*Plasmodium falciparum* and *Plasmodium vivax*—are believed to pose the greatest threat of transferring malaria. While *Plasmodium vivax* historically accounts for 80% to 90% of indigenous cases in Afghanistan and 95% of cases in Iraq, with *Plasmodium falciparum* causing the majority of the remaining cases, these numbers are likely to be inaccurate due to unreliable reporting in recent years from these war-torn areas.

According to [13], "The United States Army directs soldiers operating in these areas to consume antimalaria chemoprophylaxis and use personal protective measures, to include minimizing exposed skin through proper wear of the uniform and use of bed nets, impregnating uniforms and bed nets with permethrin, and frequently applying topical insect repellent (33% diethyltoluamide—DEET) to exposed skin. Although bed nets are an integral component of this directive, front-line soldiers, like those described in this study, may be afforded only limited protection through this measure because nighttime patrols and vigilance during dusk and dawn (when mosquitoes are prevalent) often preclude their intended use." Additionally, an injectable vaccine (RTS,S or commonly known as Mosquirix) is being evaluated in sub-Saharan Africa, in the countries of Ghana, Kenya and Malawi. Results of the pilot programs are not yet available.

The United States Army has deployed soldiers to the Central American country of Honduras for several decades, beginning in the late 1980s, to support Joint Task Force-Bravo operations in the region. JTF-B headquarters is located at Soto Cano (formerly

known as Palmerola) Air Base, Honduras, just outside the capital of Tegucigalpa. In January 1989, the 37th Engineer Battalion (Combat)(Airborne Corps) deployed as part of a task force in support of Operation *Ahuas Tara*. The unit's three-month mission was to construct a 5200-foot flight landing strip (an airfield), complete with a taxiway and parking apron, to allow C-130 aircraft to take off and land in the region. The engineer battalion's area of operations was in southwest Honduras, near the Pacific Ocean, between El Salvador and Nicaragua; its base camp was just outside the town of San Lorenzo, which lies east of the El Salvador border and north of the Bay of San Lorenzo (which feeds into the Gulf of Fonseca), a marshy region which allows the mosquito population to thrive. In addition to the airfield construction project, the engineers also conducted road construction and repair operations in the surrounding countryside. The battalion task force accomplished humanitarian projects as well, which included building an orphanage, upgrading a local school, and drilling wells to provide water for local inhabitants. Military missions involved training with the Honduran armed forces, participating in joint field operations with a host engineer battalion and conducting several airborne training operations with the Honduran Special Forces Battalion. Many American soldiers earned the Honduran Parachutist Badge after making five such jumps with the *Paracadista*.

As one might imagine, the soldiers of the 37th traveled extensively throughout southwestern and central Honduras. Malaria is known to be present throughout the country at altitudes below 1000 meters ($< 3,281$ ft), which included the 37th's Area of Operations (see Figure 2). This meant that preventive measures were taken to protect American soldiers from malaria infection. Figure 2 shows the area of operations of the battalion. This exposed the soldiers to the local population, animals, and, unfortunately, diseases.

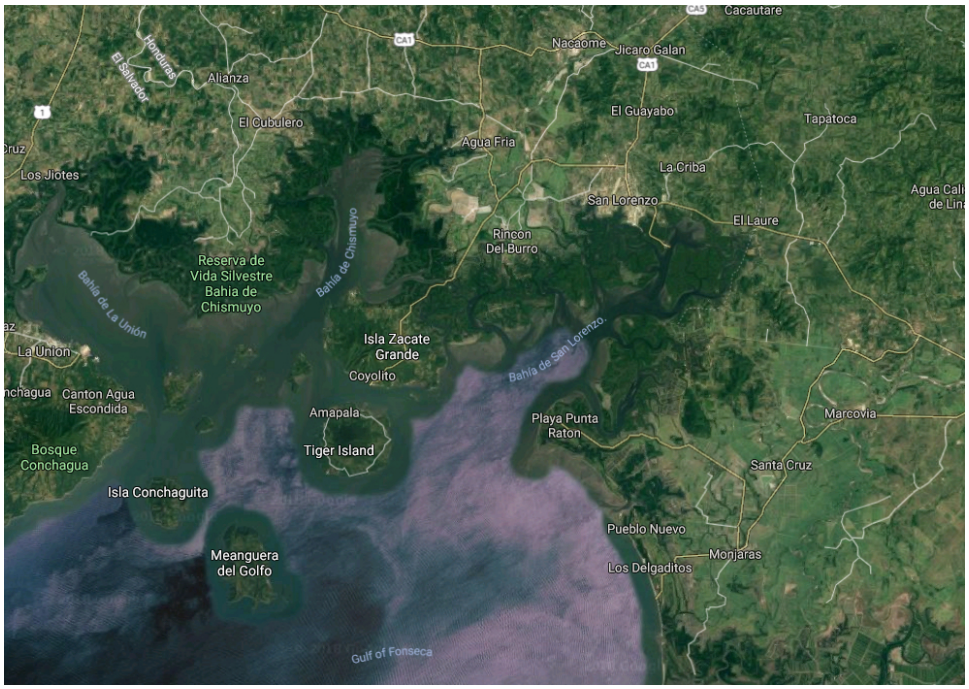

Figure 2: Area of Operations in Honduras (from [1])

Joint Task Force-Bravo is still in operation today. Its mission, "as guests of our Honduran partners at Soto Cano Air Base and as the senior representative for the United States Southern Command, maintains a forward presence and conducts and supports joint operations, actions and activities throughout the Joint Operations Area in order to enhance regional security, stability and cooperation" [11]. As such, its soldiers are exposed to the potential dangers of malaria.

This article will discuss various aspects of the disease, its spread and its treatment and the development of models of some of these aspects with differential equations. Each of the following four sections would make a nice project for an ODE class—an instructor can choose one appropriate to the level of the class. The exercises involve, respectively, exponential growth, logistics growth, systems of first-order equations and Laplace transforms. In each case students should be encouraged to dig deeper. The problems were motivated by my deployment to Central America as part of different Army operations.

2 Antimalaria Chemoprophylaxis

Malaria symptoms may include fever, chills, sweats, headache, body aches, nausea and vomiting, and fatigue [10]. Malaria symptoms will occur usually seven to ten days after being bitten (but in some cases could take up to several months) by an infected mosquito. Fever in the first week of travel in a malaria-risk area is unlikely to be malaria; however, you should see a doctor right away if you develop a fever during your trip. Malaria may cause anemia and jaundice. Malaria infections with *Plasmodium falciparum*, if not promptly treated, may cause kidney failure, coma, and death. Despite using the protective measures outlined above, travelers may still develop malaria up to a year after returning from a malarious area.

The first problem we study is one of pharmacokinetics. Malaria can be prevented through chemoprophylaxis, which basically suppresses the blood stage of malaria infections, logically preventing the disease. There are a few anti-malarial drugs currently considered for use for preventing malaria in Honduras: Atovaquone/proguanil, chloroquine, doxycycline, or mefloquine hydrochloride (see [9]). In order to understand the kinetics of any drug dosing regimen, we need to know a few things, such as the amount of the initial dosage, the drug's rate of absorption in the body, the volume of distribution, and the rate of elimination. To simplify this problem, we will assume that there is one rate of metabolism, so that we only consider one rate of elimination (each soldier's rate of absorption and rate of elimination is the same). Some pharmacists believe that malaria can be adequately prevented if three times the dosage is achieved in the bloodstream in a relatively short period and five times the dosage amount is achieved in a longer period [5, 4]. In 1989, soldiers of the 37th Engineer Battalion took one tablet of chloroquine (Aralen or its generic equivalent) once each week, usually after the Friday breakfast meal. The dosage was 300 mg per tablet. Soldiers began taking one tablet per week two weeks before deploying to the region. In this section, we will ignore the possibility of resistance to antimalarial medicines, although that can be a recurring problem [14].

Exercises

1. As a first requirement, suppose the body's system breaks down the chemicals in chloroquine at a rate that, in the absence of any new dosage, declines at a rate proportional to one-fourth of the amount of drug present. If the soldiers take the anti-malarial drug once per week, when are they getting the required dosage to prevent malaria and maintain an immunity? When is "three times the dosage" achieved? How much of the drug is in the body after several weeks (i.e., does $a(t)$ reach an equilibrium value)? Plot the amount of Aralen in the bloodstream if the regimen is continued for a half-year deployment.

2. What does the body's absorption rate x need to be to take a 300 mg tablet once each week and build up to five times the dosage (1500 mg) in the bloodstream in the long term? With this new absorption rate, when is three times the dosage achieved?

3 How Many Mosquitoes Are There?

By some estimates, in heavily infected regions, the number of mosquitoes that can be sustained by the environment is equal to one hundred million times the number of humans. For every 10 people, there are one billion mosquitoes [6]. Not all of them are capable of transmitting the disease, but one billion is a very large number.

Suppose the population $p(t)$ of mosquitoes in Central America can be modeled with the logistics equation:

$$\frac{dp}{dt} = rp\left(1 - \frac{p}{M}\right), \tag{3.1}$$

where r is the net growth rate per unit population and M is the carrying capacity of the environment. Honduras covers an area of just over 112,000 square kilometers, with an estimated population of almost eight million people. Assuming a sparse density of 60 people per square kilometer in the southwest region (the possible infected area) of the country, that would translate to a carrying capacity of mosquitoes of six billion (6,000,000,000) mosquitoes.

Exercises

1. Consider an initial mosquito population near San Lorenzo that numbers four billion. Plot and discuss the number of mosquitoes that will be present as time increases if the net growth rate per unit population is 0.1, 0.01, and 0.001.

2. What effect would lowering the carrying capacity of the environment to below the initial amount have on the population? Plot examples for both $M > p(0)$ and $M < p(0)$.

3. When is the rate of change of the mosquito population the greatest?

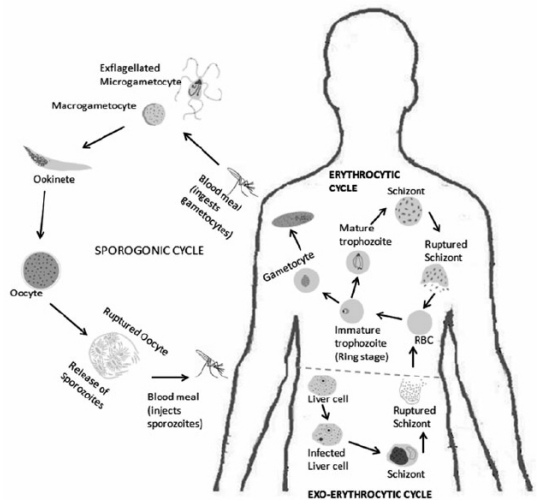

Figure 3: The malaria infection cycle (from [7])

4 Modeling Susceptibility, Infection and Recovery of Humans

One of the most important interactions being studied regarding malaria is whether immunity can be a consequence of infection. Several studies are taking place with the goal of inducing artificial immunity through the use of vaccines. These studies have led to the further investigation of the natural dynamics of immunity to the disease. According to Anderson [2, 12], both the maintenance of immunity and the degree of immunity depend on reinfections. The standard characterization of the epidemiology of malaria is what is termed an "age-prevalence" curve, which shows the proportion of each age group whose blood have the parasites present. Models are needed to study whether the effects of malaria on the human host depend on the infection's intensity, rather than whether or not the infection is present.

Malaria is caused by the multiplication of parasitic protozoa of the family *Plasmodiidae* within the blood cells of other tissues of the host. From [2]:

> Infection of a human host begins with the bite of a female mosquito and the injection of sporozoite stages into the bloodstream. These stages of the parasite are carried to the liver where they develop in the parenchymal cells. After an incubation period of several days, these exoerythrocytic stages grow, divide and release merozoites back into the bloodstream. The merozoites penetrate red blood cells, where they grow and subdivide to produce more merozoites that rupture host cells and invade other red blood cells....A portion of the merozoites develop into sexual stages, the gametocytes. Only gametocytes are infective to the mosquito. When a vector mosquito bites a human and ingests male and female gametocytes, these are freed from the blood cell, the female gamete is fertilized, and develops into an oocyst on the wall of the mosquito's gut. After 10 days or so (the actual development time is temperature-dependent), immature sporozoites migrate from the ruptured oocyst to the mosquito's salivary glands, mature to infectivity, and the cycle is ready to repeat itself. (See Figure 3 from [7].)

We could model this scenario with just two variables. For example, let $x(t)$ denote the population who have contracted a disease and $y(t)$ denote those who have not yet been exposed. If we assume that $\frac{dx}{dt}$ models the rate at which the malaria spreads, we could also assume that the rate is proportional to the number of interactions, and we get a differential equation: $\frac{dx}{dt} = kxy$, where k is a constant of proportionality that scales the number of interactions between $x(t)$ and $y(t)$.

Instead, let's study a compartment model which just treats the infection among humans. The case where everyone is born susceptible, becomes infected, and then recovers to become permanently immune has been often called the SIR model. Let $s(t)$ represent the susceptible class of the population, $i(t)$ the infected class, and $r(t)$ the recovered class. If the infection rate is α and the constant rate of recovery is β, then we can describe the dynamics of the disease by the following differential equations:

$$\frac{ds}{dt} = -\alpha s \tag{4.1a}$$

$$\frac{di}{dt} = \alpha s - \beta i \tag{4.1b}$$

$$\frac{dr}{dt} = \beta i. \tag{4.1c}$$

By scaling, we can assume that the entire population is susceptible and immediately thereafter, infection of the population occurs, and that $s(t) + i(t) + r(t) = 1$ as well, for all times t.

Perhaps a better model can be expressed as an SIRS model. Susceptible members of the population are repeatedly infected, recover, become *temporarily* immune, and then become susceptible again. Introduce γ as the average rate of movement out of the immune state. In other words, it is the inverse of the average time spent with immunity. The coupled differential equations become:

$$\frac{ds}{dt} = \gamma r - \alpha s \tag{4.2a}$$

$$\frac{di}{dt} = \alpha s - \beta i \tag{4.2b}$$

$$\frac{dr}{dt} = \beta i - \gamma r. \tag{4.2c}$$

4.1 Exercises

1. Plot solutions to the system of equations (4.1). Use typical values for α of 2 year^{-1}; allow β to vary between 0.07 and 0.03 year^{-1}. Use Equations 4.1 to plot the solutions for each class. Assume, with scaling, that the initial population is 100% of the soldiers and that five percent are infected when the study begins.

2. Plot solutions to the system of equations (4.2). Let $\beta = 0.5$ year^{-1} and $\gamma = 0.5$ year^{-1}. The parameter α can vary between 0.2 and 5 year^{-1}. Further, an important assumption is that the parameters β and γ are independent of the parameter α. Explain why. As α increases, what happens to the immunity of the population?

5 Controlling the Mosquito Population

Let's examine a small part of the base camp; in particular, we will model the number of mosquitoes that existed in the area of the battalion tent city. Imagine that we could track the number of mosquitoes with some device. Assume that the mosquito population in the area surrounding the tents grows at a rate of 5% per day. They are drawn to the living quarters by many factors. To combat the mosquitoes, the operations section of the battalion tasks a platoon to spray insect repellent throughout the area. This causes a 1000-mosquito drop in the population over the next 24 hours after spraying. The platoon sprays the area on the 3rd, 6th, 9th, 12th, etc., days after the operations section begins tracking mosquitoes.

Exercises

1. If there are initially 5000 mosquitoes, what happens to the population over time? Approximately how many mosquitoes will there be after two weeks? Plot both the effects of the spraying (the forcing function) and the overall mosquito population.

2. Is this strategy effective or should it be adjusted, and how?

6 Some Solutions to Exercises

Note for Instructors

These are problems used in an introductory course in Differential Equations. In the first section, a simple, first-order equation is used to model and predict the amount of drug in the bloodstream. The twist involves finding the absorption rate. The second section involves a logistics equation for modeling rates of change for populations. The third section uses the well-known SIR and SIRS models and is effective for incorporating computer-algebra systems to see long-term behavior. The instructor could also adjust the equations to introduce interaction. The final section involves the use of Laplace transforms to model and solve. In each section, try to incorporate student writing to add to the solutions.

Section 2: Antimalaria Chemoprophylaxis

1. First, let's assume a continuous situation and that small variations for individual soldiers can be ignored. Let $a(t)$ equal the amount of drug in the bloodstream (measured in mg) at time t (measured in weeks). The soldiers take 300 mg each week for two weeks before deploying. The initial value problem is

$$\begin{aligned} \frac{da}{dt} &= -\frac{1}{4}a + 300 \\ a(0) &= 300 \end{aligned}$$

Solving, we obtain $a(t) = 1200 - 900e^{-t/4}$. Plot this. Each soldier should have 900 mg in the bloodstream at approximately $t = 4.39$ weeks, or sometime between the second and third week after arrival in country. After 10 weeks ($t = 12$) in country, $a(12) = 1155.19$ mg, closing in on the equilibrium value of 1200 mg.

2. In order to reach an equilibrium point of five times the 300 mg dosage, the amount of drug needs to get to 1500 mg, so the rate needs to decline (so the body retains more drug). At equilibrium, $a(t) = 1500$ and $\frac{da}{dt} = 0$, so we solve $0 = x * 1500 + 300$ for x, obtaining $x = -0.2$. Solving

$$\begin{aligned} \frac{da}{dt} &= -\frac{1}{5}a + 300 \\ a(0) &= 300 \end{aligned}$$

we find $a(t) = 1500 - 1200e^{-\frac{t}{5}}$. Each soldier should have 900 mg in the bloodstream at approximately $t = 3.47$ weeks, or sometime between the first and second week after arrival in country.

Section 3: How Many Mosquitoes Are There?

1. Solve Equation (3.1) with $M = 6{,}000{,}000{,}000$ and the three net growth rates. With the highest rate ($r = 0.1$) we obtain

$$p(t) = \frac{12000000000}{2 + e^{-\frac{t}{10}}}$$

A plot is shown in Figure 4. Solve the logistics equations with the other values of r. As r decreases, so does the number of mosquitos over time. For Requirements 2 and 3, try various values for M and discuss the behavior.

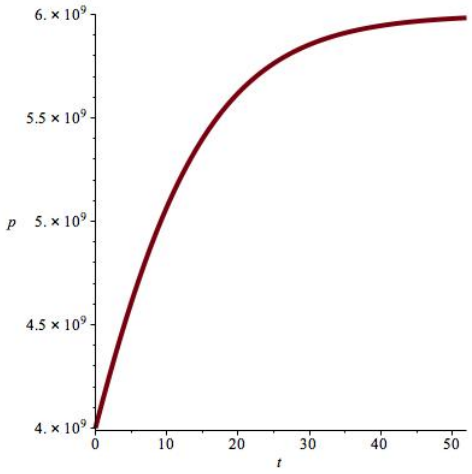

Figure 4: The population of mosquitos with $r = 0.1$

Section 4: Modeling Susceptibility, Infection and Recovery of Humans

1. Using Equations (4.1abc) with the values provided, the behaviors for each class over a 20-week period are shown in Figure 5a.

2. Using Equations (4.2abc) with the values provided (start with $\alpha = 2.5$), the behaviors for each class over a 20-week period are shown in Figure 5b. Vary the parameters to see how the behaviors change.

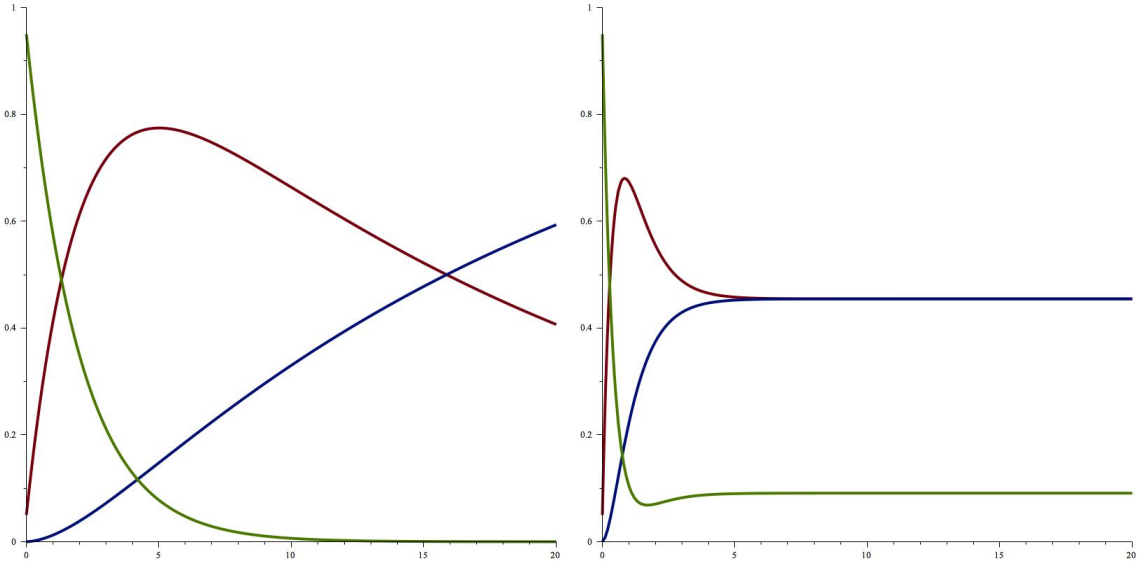

Figure 5: The susceptible (green), infected (red), recovered (blue) populations using the SIR model (4.1) on the left, and the SIRS model (4.2) on the right.

Section 5: Controlling the Mosquito Population

1. We assume that it takes 24 hours for the spraying to have an effect, so it appears to be an instantaneous reduction in the number of mosquitos. The forcing function (caused by the spraying) can be viewed as a step function, as seen in Figure 6.

   Define $m(t)$ to be the number of mosquitos in the base camp at day t. The differential equation becomes

   $$\frac{dm}{dt} = 0.05M + \text{forcing}$$

   Using Laplace transforms, we solve the differential equation with an initial condition of $m(0) = 5000$. A plot of the solution is shown in Figure 7. After 14 days with this scenario, there are approximately 4593 mosquitos in the base camp.

2. There appears to be a downward trend in Figure 7, but it might not be drastic enough. In some sense, it almost keeps the mosquito population in a status quo. Possible recommendations include increasing the frequency of spraying, finding an alternative to spraying that might be more effective, etc. Students can discuss environmental issues as well.

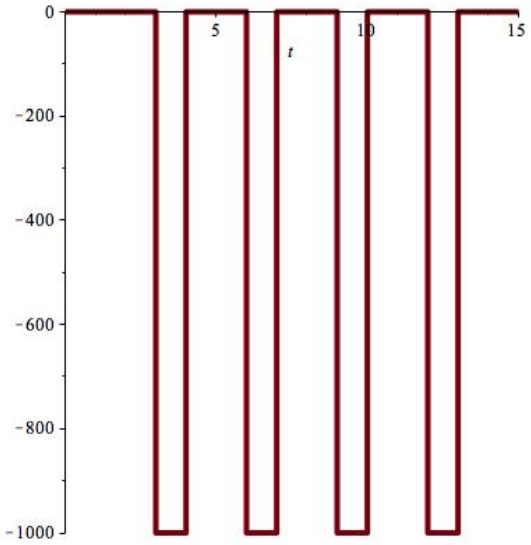

Figure 6: The forcing function

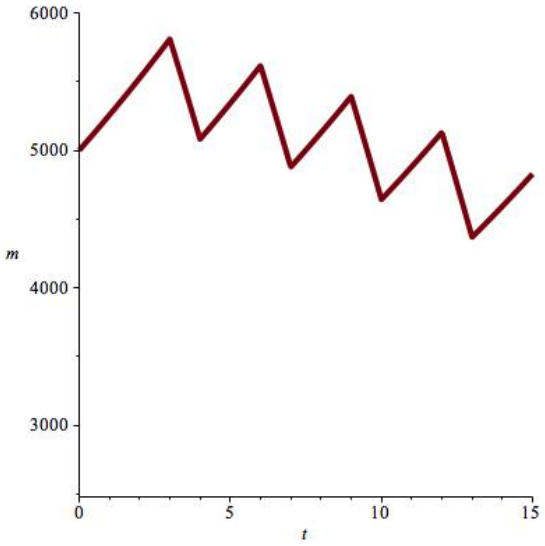

Figure 7: The number of mosquitos in the base camp

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