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A Comprehensive Model of Spread of Malaria in Humans and Mosquitos

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***Abstract*—Mathematical models have the capability to incorporate statistical data so that infectious diseases can be studied in-depth. In this article, we use mathematical modeling to study malaria through a combination of the Susceptible, Exposed, Infectious and Recovered (SEIR) Model for humans; Susceptible, Exposed and Infectious (SEI) Model for mosquitos; and the Four Stage Life Cycle Model of the mosquito. Due to the fact that malaria is spread to humans through the bite of a female mosquito that has been infected by the plasmodium parasite, the impacts of mosquitos are also studied in this paper using the SEI Model. Finally, the growth of the mosquito population is directly related to the spread of malaria, the Four Stage Life Cycle is incorporated to model the effects of climate change and interspecies competition within the mosquito life cycle stages of Egg, Larvae, and Pupae. The combination of these models are used to show the growth and spread of malaria.**

I. Introduction

Scientists have studied malaria transmission for over 100 years in hopes of finding a method of eradication. Malaria is still wide spread with the possibility of becoming a major source of death in certain areas[1]. According to the latest estimates, globally there are 198 million cases of malaria in 2013 and the disease has led to approximately 584,000 deaths in Africa [2]. Poverty, environment, and climate play major roles in the spread of the disease. The cause of malaria stems from the parasite *plasmodium falciparum*. This parasite inhabits female mosquitoes who then infect humans through biting. The disease is not communicable from human to human; however, if an infected human is bitten by a non-infected, susceptible mosquito, that mosquito may then become infected.

The study of malaria began with Sir Ronald Ross Ross[1]. In 1911, he developed the Ross Model (a very basic version of the current SEIR Model) whose parameters are shown in Table I. Later models, such as the Anderson and May model added the parameters of per capita rate of human mortality, latency, and immunity to the parameters developed by Ross[1].

TABLE I. Ross Model Parameters

Symbol	Parameter Description
a	Man biting rate
b	Prop of bites that produce infection in human
c	Prop of bites by which a susceptible mosquito become infected
m	Ratio of number of female mosquitos to that of humans
r	Average recovery rate of human
μ_1	Per capita rate of human mortality
μ_2	Per capita rate of mosquito mortality
τ_m	Latent period of mosquito
τ_h	Latent period of human
i	Immunity

Even with the numerous models and studies already in place, it is very difficult to have a thorough knowledge of all parameters that cause the spread of malaria. *"Such understanding can only be reached by synthesizing the many factors controlling transmission, integrating detailed biological information into one coherent picture [3]."* To address this issue, we have developed a more comprehensive model which includes spread of malaria in humans, mosquitos and how mosquito population impacts spread of malaria.

In summary, we first look at the related works and the studies that have been conducted in this field. Then, we discuss our methodology which includes: the SEIR Model, SEI Model, and the Four Stage Life Cycle of the Mosquito and the parameters used in these models. Next, the experiments are discussed in context to various models by using already established values for different parameters. Finally, this paper shows the results obtained from our model and discusses topics for future research in the study of malaria.

II. Related Works

To model malaria properly, accurate statistics are necessary. In [4], the importance of diagnosing malaria in humans is shown. Malaria diagnosis is usually done in a passive way - only those patients exhibiting malaria symptoms are tested. For malaria to be modeled effectively, any patient with a possible exposure to malaria needs to be tested, so that accurate statistics can be documented and, so that, treatment can begin while still in the early stages of the disease.

While injections play a key role in the management of malaria, the injections are costly [5] and over time become ineffective against the disease. Other forms of prevention include insecticides and nets. Insecticides also become ineffective over time as malaria evolves to withstand the combatants. Mosquito nets appear to be the best and longest lasting form of prevention, and also does not cause a mutation in the disease. However, the prevention doesn't help us gain insight on how malaria spread from mosquitos to humans and among mosquitos.

When prevention methods such as injections, insecticides, or larvacides [6] are used, there is a following period called **interruption of transmission**. *"Because interruption of transmission is a stochastic event, its occurrence depends on population size, as well as on R_e"*(where R_e is the reproduction number)[7]. When the interruption in transmission occurs an immediate decrease in immunity follows, and in turn this causes an eventually increase in those infected by the disease. The state of disease requires close monitoring, so that in the

event of an interruption in transmission occurs a population's immunity can be artificially increased. This study highlighted the importance of stochastic events but fails to design a comprehensive model.

The main objective of some studies of malaria is disease management and control. The authors of [8] show that mathematical models give large amounts of significant data to not only provide information on the disease itself, but also give insight and predictions into the outcomes of alternative courses of action. While the ability to study current prevention methods and their outcomes is necessary; it is important to go further and predict what effects new methods might have on the disease. For example, if insecticides are used to rid of an area of mosquitos, over time, humans in that area would lose the resistance they had built up while the mosquitos were present and biting. This loss of resistance and the methods by which the resistance is lost needs to be documented and studied to prevent future outbreaks in the event that the insecticide is no longer working.

While most papers agree on the basic parameters necessary for the modeling of malaria growth and immunity, the authors of [9], state that the most important parameter for initial disease transmission is the mosquito biting rate. This rate is determined by multiple other parameters, including: mosquito birth rate, density-dependent mosquito death rate, and human rate of recovery. The second most important parameter for equilibrium disease prevalence in areas of high transmission is stated as the human rate of loss of immunity. While all other parameters remain consistent, loss of immunity evolves with the measures taken to combat it and it is this variable that determines the growth and spread of malaria. They also determined that the knowledge gained from the research of malaria is used in other areas of study, including determining the cost-effectiveness and usefulness of combatants being used in the prevention of malaria.

In [10], the authors focus on *Recovered* individuals who return to the *Susceptible* stage and the length of immunity they experience. Their paper is devoted to the basic idea that, relapse rate must be decreased for a prolonged period to increase the recovery rate. The main parameters used include relapse rate and recovery rate. Yet, in working with recovery, another study [11] shows the importance of vaccinations which has not been mentioned in this article. Since, no one vaccine can cure malaria, the vaccines must be geared toward creating longer immunity intervals and be modeled in the system.

Another area of study in the eradication of malaria is directly associated with mosquito re-population. Mosquitos are genetically altered in labs, then released into areas where malaria is prevalent. These genetically modified mosquitos will be the descendants of mosquitos that have been developed to have a natural immunity to the disease and are incapable of carrying or spreading the disease. When these mosquitos reproduce in the wild, their offspring will also have the same characteristics [12].

In [13], the importance of modeling the life stages of the mosquito are noted. Not merely the susceptibility of the mosquito to malaria is necessary, but the life cycle and the factors that aid or prevent the growth of the mosquito population are also important. In this work, the mosquito life cycle is divided into two classes - larvae and adult. The class of larvae consists of three subclasses, which include: eggs, larva, and pupa. Parameters involved in the development of the larvae class include rainfall and intra-specific competition. This study is used within this paper to develop the *ELP* Model.

The authors who used dynamical analysis of SEIR of an epidemic model [14] tried the perturbation method to get an analytical solution of the SEIR model. They then uses the statistics obtained from the model to compare the exact solution and the analytical solution. But in our paper, we focus on the dynamical analysis rather than the perturbation method. The perturbation method involves using nonlinear problems to develop numerous linear sub-problems and ending with the solutions to give approximate solutions.

III. Methodology

Using compartmental modeling [15] represented as a set of differential equations, the dynamics of malaria are modeled. The SEIR model is the first one we have defined and implemented. This model simulates the effect of the disease on humans. The SEI model is then designed to simulate the spread of malaria on mosquitoes. Finally, the Four Stage Life Cycle Model is used to add the importance the growth of the mosquito population has on malaria.

A. Model 1: The SEIR model of humans

The SEIR Model can only be representative of humans due to the final compartment *Recovered* or *R*. Once an individual recovers from malaria, they can become susceptible, again. Immunity to the strain of malaria from which they recovered will last, but the variations in the strains may cause the infection to be reproduced. The human SEIR model suggested by [16] is shown in Figure 1.

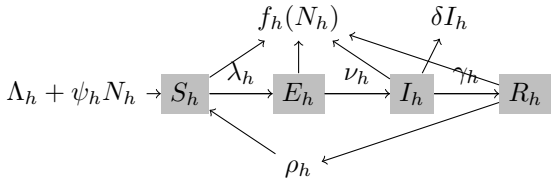


Fig. 1. Human Model of SEIR [16]

This model shows that given the immigration rate of humans (Λ_h) and adding birth rate, as well as the current total population, *Susceptible* population is calculated. From the *Susceptible* state, the per capita density-dependent death and emigration rate for humans is taken out($f_h(N_h)$); and λ_h (infection rate for humans) is used to compute the size of population in the *Exposed* state. From there, the per capita rate of progression of humans exposed (ν_h) to the malaria is used to compute the size of population in the *Infectious* state; and the per capita disease-induced death rate(δ) for humans is taken out of the model. Finally, the per capita recovery rate (γ_h) is used to compute the number of people in the final stage of *Recovered*. At the *Recovered* stage, then per capita rate of loss of immunity (ρ) for humans is computed sending some *Recovered* back to the *Susceptible* stage. The model can be represented as a set of differential equations.

$$\frac{dS_h}{dt} = \Lambda_h + \psi_h N_h + \rho_h R_h - \lambda_h(t) S_h - f_h(N_h) S_h$$

$$\frac{dE_h(t)}{dt} = \lambda_h(t) S_h - \nu_h E_h - f_h(N_h) E_h$$

$$\frac{dI_h}{dt} = \nu_h E_h - \gamma_h I_h - f_h(N_h) I_h - \delta_h I_h$$

$$\frac{dR_h}{dt} = \gamma_h I_h - \rho_h R_h - f_h(N_h) R_h$$

where:
$N_h = S_h + E_h + I_h + R_h$

$f_h(N_h) = \mu_{1h} + \mu_{2h} N_h$

$\lambda_h = b_h(N_h, N_v)\beta_{hv} \frac{I_v}{N_v}$

$b_h(N_h, N_v) = \frac{\sigma_v N_v \sigma_h}{\sigma_h N_h + \sigma_h N_h}$

Parameters of this model are listed in the Table II

TABLE II. PARAMETERS OF SEIR MODEL

Symbol	Parameter Description
Λ_h	Immigration rate
λ_h	P/capita infection rate
ψ_h	p/capita birth rate
σ_h	Max no. of mosquito bites p/unit of time
β_{hv}	Probability of transmission from M to H
ν_h	p/capita rate of progression from Exp to Inf
γ_h	p/capita recovery rate
δ_h	p/capita disease-induced death rate
ρ_h	p/capita rate of loss of immunity
μ_{1h}	density IND part of death/emigration rate
μ_{2h}	density dep. part of death/emigration rate
σ_v	Times 1 mosquito would bite a human p/unit of time
b_h	per capita birth rate of human

B. Model 2: The SEI model of mosquitos

Using the same strategy of developing compartments, the model for mosquitos has been designed. The compartments are: Susceptible - Exposed - Infected (SEI). Since, the mosquitos can't be treated of malaria, so we assume that all the infected mosquitos eventually die and this assumption is coherent with other studies [17]. Figure 2 shows the model.

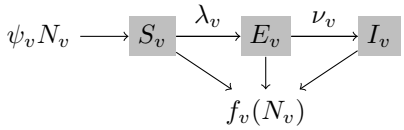


Fig. 2. Mosquito Model of SEI[16]

NOTE: An avid reader can see that the above presented model is quite similar to the previous one, but the an exception that the X_v is used to represent the mosquito.

The set of differential equations representing the SEI model are shown below:

$$\frac{dS_\nu}{dt} = \psi_\nu N_\nu - \lambda_\nu(t) S_\nu - f_\nu(N_\nu) S_\nu$$

$$\frac{dE_\nu}{dt} = \lambda_\nu(t) S_\nu - \nu_\nu E_\nu - f_v(N_\nu) E_\nu$$

$$\frac{dI_\nu}{dt} = \nu_\nu E_\nu - f_\nu(N_\nu) I_\nu$$

where:
$N_v = S_\nu + E_v + I_v$

$f_v(N_v) = \mu_{1v} + \mu_{2v} N_v$

$\lambda_v = b_v(N_h, N_v)(\beta_{vh} \frac{I_h}{N_h} + \tilde{\beta}_{vh} \frac{R_h}{N_h})$

$b_v(N_h, N_v) = \frac{\sigma_v N_h \sigma_h}{\sigma_v N_v + \sigma_h N_h}$

Description of the parameters of this model is given in Table III

TABLE III. PARAMETERS OF SEI MODEL

Symbol	Parameter Description
λ_v	P/capita infection rate of mosquito
ψ_v	Per capita birth rate
σ_v	Times 1 mosquito would a human p/unit of time
β_{vh}	Probability of transmission from infected human to susceptible mosquito
$\tilde{\beta}_{vh}$	Probability of transmission from recovered human to susceptible mosquito
ν_v	p/capita rate of progression from Exposed to Infected
μ_{1v}	density independent part of death rate
μ_{2v}	density dependent part of death rate
b_v	per capita birth rate of mosquito
σ_h	Max no. of mosquito bites p/unit of time

C. Model 3: The ELP model of mosquitos

The final piece of model design in this paper involves the connection of the mosquito life cycle stages to the growth and spread of malaria. The mosquito life cycle is broken down into four stages: *Eggs (E), Larvae (L), Pupae (P), and Adult*. The model is represented as follows:

$$\frac{dE}{dt} = A_r e_p - E(T_e + M_e)$$

$$\frac{dL}{dt} = ET_e - L(T_l + M_l) - K_0 L^2$$

$$\frac{dP}{dt} = LT_l - P(T_p + M_p)$$

where A_r is the reproducing adult mosquitos, e_p is the number of eggs per oviposition, T_e is the time taken for an egg to develop, M_e is the egg mortality rate, K_0 is the carrying capacity term, T_l is the larval development time, T_p is the pupal development time, M_p is the pupal mortality, and M_l is the larval mortality. Further details of the parameters can be found in [18]. The parameters involved infer that geo-climate and interspecies competition determine the growth rate of the mosquito population which, in turn, determines the rate at which malaria spreads. We implemented this model prior to the implementation of SEIR and SEI models in order to show the importance of the mosquito population on malaria.

IV. EXPERIMENTATION

There are three models and these models interact with each other. We implemented the ELP model first because we assume that the output of this model provides us the input, i.e., the mosquito population of the SEI model. We used the R_h from the SEIR model to the compute transmission rate λ_v of mosquitos in the SEI model. So, we will introduce the experimentation related to ELP first, then SEI and finally the SEIR. Also, the initial parameter values for this comprehensive models are listed in Table IV.

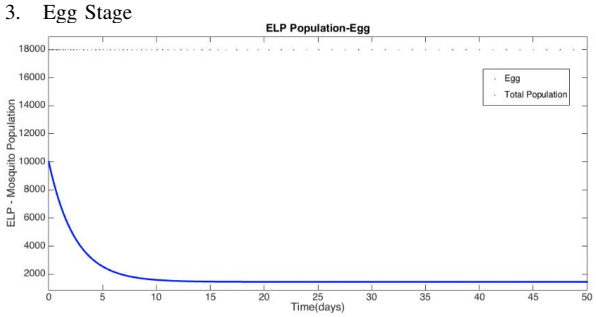
TABLE IV. GENERIC PARAMETER VALUES

Parameter	Parameter Value
$Time_{SEIR}$	0-1000
$Time_{ELP}$	0-50
$Time_{SEI}$	0-100
POP_H	560
POP_M	2500
POP_{ELP}	18000
$[E-L-P]$	[10000-5000-3000]
$[S-E-I]$	$[P*0.8-S*0.02-E*0.0001]$
$[S-E-I-R]$	$[500-50-10-5]$

TABLE V. ELP PARAMETERS [18]

Symbol	Parameter Description	Values
A_r	Reproducing adults	20
e_p	Eggs per oviposition	30
T_e	Egg development time	0.361
M_e	Egg mortality	0.05
K_0	Carrying capacity term	$2*10^-4$
T_l	Larval development time	0.134
T_p	Pupal development time	0.342
M_p	Pupal mortality	0.0025
M_l	Larval mortality	0.0501

Fig. 3. Egg Stage



A. Model 1: The EPL model of mosquitos

In this model, we use various parameter values as suggested in [18] for the ELP Model. These are listed in Table V.

Figure 3 represents the Egg stage of the mosquito life cycle. In this representation not all eggs will survive to the next stage of *Larvae*, that is why, we see a drop in the number of eggs as the time progresses. Figure 4, represents the *Larvae* and *Pupae* stages. These stages will also lose population due to various factors including interspecies competition and rainfall. Figure 5, represents the ELP stages as a whole.

Fig. 4. Larvae and Pupae Stages

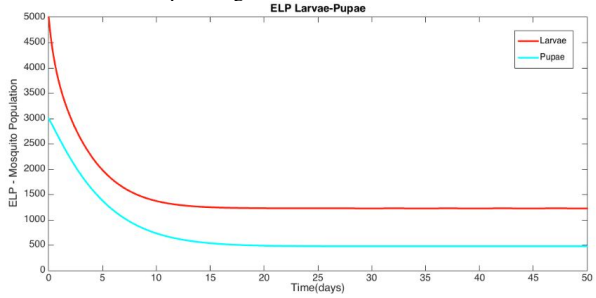
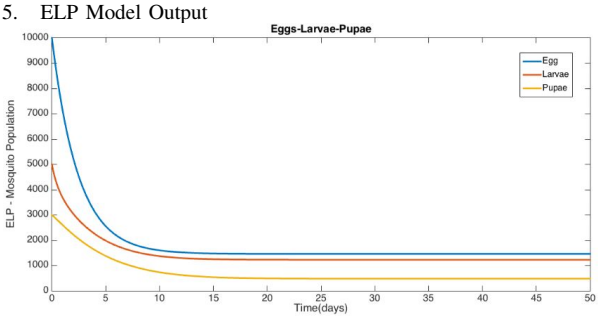


Fig. 5. ELP Model Output



B. Model 2: The SEI model of mosquitos

In this model, we use various parameters suggested in [16] for the SEI Model. These are listed in Table VI.

TABLE VI. PARAMETERS OF SEI MODEL

Symbol	Parameter Description	Values
λ_v	P/capita infection rate of mosquito	**See Model 2**
ψ_v	Per capita birth rate	80
σ_v	Times 1 mosquito would a human p/unit of time	0.6000
b_{hv}	Probability of transmission from M to H	2.000×10^{-2}
b_{vh}	Probability of transmission from H to M	0.8333
ν_v	p/capita rate of progression from Exp to Inf	0.1000
μ_{1v}	density IND part of death rate	0.1429
μ_{2v}	density dep. part of death rate	2.279×10^{-6}
b_v	per capita birth rate of mosquito	**See Model 2**

Fig. 6. Susceptible Stage

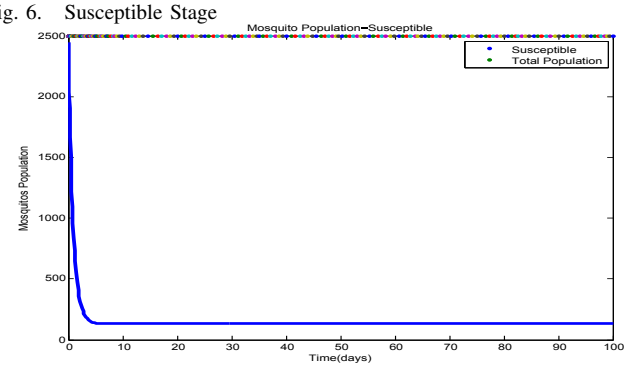


Figure 6, represents the *Susceptible* stage of the population. In this experimentation, we used a total population count of 2500 to begin the process. The number of *Susceptible* mosquitoes was calculated by multiplying the total population by the per capita birth rate.

Fig. 7. Exposed and Infected Stages

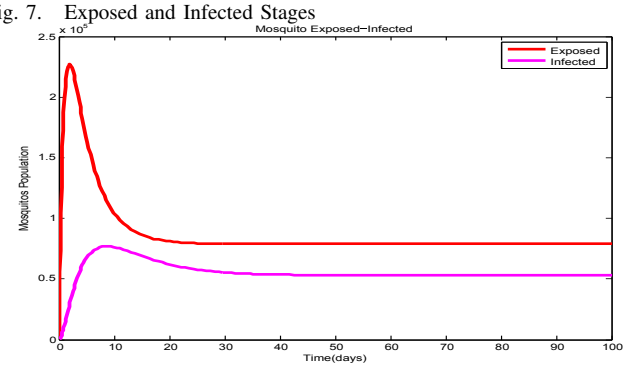


Figure 7, represents the increase in *Exposed* and *Infected* for mosquitos. The *Exposed* group is calculated by multiplying the *Susceptible* population by the infection rate (λ_v) over a given period of time, subtracting the per capita rate of progression from *Exposed*

to *Infected*, and subtracting the expected death rate ($f_\nu(N_\nu)$ of the total population.

The *Infected* population is calculated by subtracting the death rate (f_ν) of from those included in the per capita progression rate (ν_ν) of the *Exposed* stage.

C. Model 3: The SEIR model of humans

In this model, we use various parameter suggested in [16] for the SEIR Model. These are listed in Table VII.

TABLE VII. PARAMETERS OF SEIR MODEL

Symbol	Parameter Description	Values
Λ_h	Immigration rate	**See Model 1**
λ_h	P/capita infection rate	3.285×10^{-2}
ψ_h	p/capita birth rate	7.666×10^{-5}
σ_h	Max no. of mosquito bites p/unit of time	18
b_{hv}	Probability of transmission from M to H	2.000×10^{-2}
b_{vh}	Probability of transmission from H to M	0.8333
ν_h	p/capita rate of progression from Exp to Inf	8.333×10^{-2}
γ_h	p/capita recovery rate	3.704×10^{-3}
δ_h	p/capita disease-induced death rate	3.454×10^{-4}
ρ_h	p/capita rate of loss of immunity	1.460×10^{-2}
μ_{1h}	density independent part of death/emigration rate	1.6×10^{-5}
μ_{2h}	density dep. part of death/emigration rate	3.0×10^{-7}
b_h	per capita birth rate of human	**See Model 1**

Fig. 8. Susceptible Stage

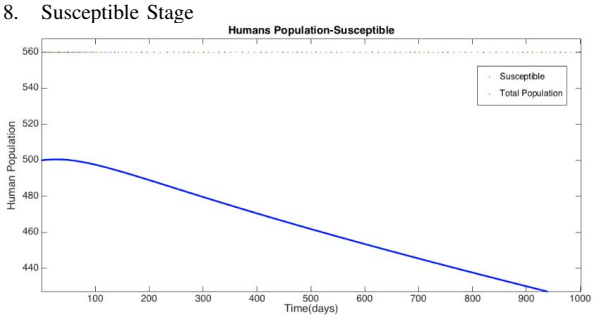


Figure 8, represents the *Susceptible* stage of humans, which shows that, over time, the *Suseptibles* decrease. The calculation for those *Susceptible* is the addition of immigration rate (Λ_h) to the total population multiplied by the per capita birth rate ($\psi_h N_h$) subtracted by the per capita rate of infection (λ_h) of the *Susceptible* group and the death rate (f_h) of the *Susceptible* population .

Fig. 9. Exposed, Infected, and Recovered Stages

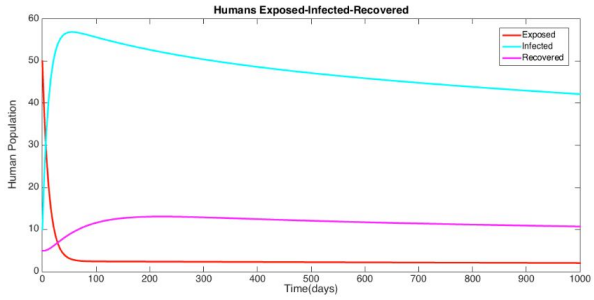
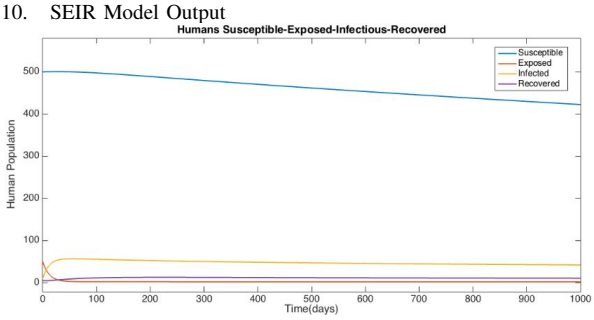


Figure 9, represents the *Exposed*, *Infected* and *Recovered* stages. From the figure *Exposed* decreases, *Infected* Increases and *Recovered* increases at a smaller rate. The *Exposed* population is the product of the per capita infection rate (λ_h) of the *Susceptibles* over a given period of time subtracted by the per capita rate of progression (ν_ν) of the *Exposed* population and the death rate (f_h).

The *Infected* population was determined by the subtraction of the per capita recovery rate (γ), death rate (f_h), and per capita disease-induced death rate (δ_h) from those in the per capita rate of progression (ν_ν) the from *Exposed* population. The final piece of Figure 9, the *Recovered* population is calculated by subtracting the per capita rate of loss of immunity (ρ_h) and the death rate (f_h) from the per capita recovery rate (γ_h) of the *Infected* stage. Figure 10, represents the combine SEIR as a whole[1].

Fig. 10. SEIR Model Output



V. FUTURE WORK

Future work will include modeling the effects of immunizations on the evolution of the disease. The disease evolves in response to medicine; therefore, immunizations become ineffective over time and new immunizations will need to be developed continually to combat new strains of the disease. Currently, there is no complete cure for malaria in vaccination form - largely due to the numerous factors that aid the spread of the disease [19].

VI. CONCLUSION

In conclusion, malaria's spread and growth rate can be based on the current mosquito population, human response to mosquito bite and also how mosquito's birth progression. The SEIR model representing human and SEI model representing mosquito are implemented and, given current statistics, the human and mosquito population stages of malaria are modeled effectively. Forming a connection between the ELP Model and the SEI Model, adds an additional layer to the outputs. The ELP model is used to approximate the total mosquito population and, from there, the SEI model can be based on that population. Bringing all of these parameters and models together, it is possible to show how humans are effected currently, as well as, future approximations given different inputs.

VII. AUTHORS CONTRIBUTION

AT and PT developed the manuscript; CJ and SG implemented the models; PT lead the brainstorming sessions and provided the idea of comprehensive model of malaria. VM supervised all aspects of the project and provided insight into modeling of diseases using PDEs.

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