Dengue fever continues to be a worldwide health and economic problem, with an estimated 80 million people being infected annually. Currently, no specific treatment exists for infected patients. This project will be an attempt to quantify the effects of certain aspects of the virus. For example, it may be more productive to reduce the rate at which the virus infects host cells than to increase the death rate of the virus. This sort of knowledge may serve as a guide for the development of more effective treatments. The goal of this project will be to develop a mathematical model of the dynamics of the infection and then use the model to gain insight into different treatment strategies.

Where will the results be published, exhibited or performed? The results will be presented at the national meeting of the American Mathematical Society (January 2014) and at the sectional meeting of the Mathematical Association of America (March 2014). They will be published in one of the following journals: Mathematical Biosciences, Journal of Biological Dynamics, Bulletin of Mathematical Biology.

What other sources of funding (internal and external) have you identified for this project? None

List years and amounts of prior Loyola University faculty grants (for the last three years): None

Does your research involve human subjects? Yes _x_ No. If yes, funding for this project is contingent on receiving IRB approval. If you have IRB approval prior to submitting your proposal, please attach the approval memo to your application. If you do not have IRB approval at the time of your submission, please complete the IRB protocol as soon as possible after your proposal submission.
Project Narrative:

Dengue fever infection begins when a human is bitten by a mosquito carrying the virus. Once the virus enters the blood stream, it seeks out a specific type of white blood cell, namely the mononuclear phagocyte (monocyte). These cells have several immune functions and are an essential part of the body's defense against pathogens. Once the virus has infected a monocyte, it reproduces for a time. Later, the infected cell dies and releases more of the viruses into the blood stream and the process continues. One of the main functions of the monocyte is to replenish the body's macrophage (another type of white blood cell) population. These are the cells that typically engulf and destroy undesired pathogens throughout the body. So, before macrophages can play their role in eliminating the viruses, they must first survive a phase where they themselves are susceptible to infection. The goal of this project will be to accurately describe this process mathematically so that the disease can be studied through numerical simulation.

While it is difficult to estimate the number of global infections of the dengue virus annually, this figure has been said to be at least 80 million [11]. In the Americas, dengue epidemics date back to 1780 in Philadelphia and have continuously affected both North and South America since. In many Asian countries, dengue haemorrhagic fever remains a serious problem among children, causing an estimated 100,000 deaths in 1995 [10, 11]. While deaths are uncommon in adults, the economic impact of the 1981 Cuban epidemic alone is estimated at US$ 103 million [7, 8]. Most efforts to control epidemics are focused on controlling the population of the principle vector, the Aedes aegypti mosquito. There is currently no specific treatment for dengue infection and the development of a vaccine has remained elusive [7, 9, 12]. It is in this aspect (treatment) that I wish to contribute in this project. Recently, the alkaloidal fraction of Uncaria tomentosa, a vine native to the Amazon and Central American rainforests, has been effective in reducing monocyte infection rates by the dengue virus [12]. This could be a clear treatment technique that might help reduce the length of infection endured by patients. But, one could also imagine treatments that might work in other ways. For example, another treatment approach might be effective in reducing the replication rate of the virus within infected monocytes. One naturally wonders if one approach would be more effective than another. These are examples of questions that can be addressed through the use of mathematical models. Indeed, in [13], a model was shown to predict that in the case of malaria, reducing the replication rate was more effective than reducing the infection rate. Optimal treatments for malaria infection were also theoretically obtained in [14]. In that work, it was shown that periodic treatments that are in synchronization with the natural periodic bursting rate of red blood cells infected by malaria are optimal.

There are very few (less than 50) mathematical studies of dengue fever. Of those, all but one [9] are concerned with the dynamics of the spread of the disease from person to person [4, 5]. We will be concerned with the dynamics within an individual infected with the virus. The primary host target for the dengue virus is the monocyte. In [9], it is assumed that the production of monocytes within the bone marrow is constant. This may be more or less the case under normal circumstances in a healthy individual, but one would expect that the monocyte population would be significantly affected by nearly any
parasitic infection. Indeed, it was shown in [6] that there is increased apoptosis (self-destruction) in human monocytes when infected by the dengue virus. This will clearly cause the production rate of monocytes to vary. For this reason, a more descriptive mathematical model is needed in order to make accurate predictions. The two months funded by this fellowship would be solely dedicated to this task. I have had past experience modeling the within-host dynamics of blood parasites. Namely, I have published two papers on malaria infection [13,14] and have submitted another that is currently being reviewed [1]. The techniques used in those papers will also be applicable to dengue fever. Since monocyte production is not constant, their production will be modeled by a size-structured population model which will take the form of a system of hyperbolic first-order partial differential equations. The dynamics of the virus population will be modeled by a system of ordinary differential equations. This combination of partial and ordinary differential equations in one model has proven successful in describing other blood diseases [13, 14], and is suitable for dengue fever as well. The modeling process is an iterative one. A considerable amount of time is spent becoming familiar with as many details of the phenomenon as possible. One also has to attempt not develop a model that is more complicated than necessary since computation can become overly cumbersome. Once an initial model is developed, it is compared with available data and an assessment is made on its agreement with this data. The data in [6] will be particularly useful in estimating parameters of the model using techniques that I have been successful with [3]. If the results are unsatisfactory (they usually are at first), more research is done and the model is modified. This process continues until a model is developed that is a good balance of simplicity and accuracy. I do expect that developing a model of dengue infection will be significantly more difficult than it was to develop the malaria model because the production of monocytes is much more complicated than the production of red blood cells (the host of the malaria parasite). Still, I am confident that I will be successful in producing an accurate mathematical description of the process, which will surely merit a journal publication.

Recently, I have participated in developing more accurate numerical methods for solving the models previously mentioned [1, 2]. The development of the model will require numerical simulation, which is an area where students can participate in this research. There are several students on campus who I believe already have the programming skills to participate in this project and I plan on actively seeking one of them out. I have had success in publishing with undergraduates in the past [14], and I expect to have a student’s name on this publication as well.

I do not expect to be able to submit the manuscript until October 2013. I expect to present the results submitted for publication at the annual national meeting of the American Mathematical Society in January 2014. I also expect to have a student present their work at the annual sectional meeting of the Mathematical Association of American, in March 2014.

Bibliography


Project Timeline:

**May 13-June 13 2013:** This month will be dedicated to an intense literature search and the initial modeling phase. Gathering available data will be an important prerequisite to developing an initial model. Testing the model will require significant time writing computer programs that implement numerical schemes to approximate solutions of the model. By the end of the month, the general form of the model should be close to satisfactory. Between June 10 and June 13, I will attend the annual meeting of the Society for Mathematical Biology and I plan to present preliminary results. Should I run into serious problems developing a reliable model, I will be able to consult with experts in the field of disease modeling at this conference and acquire a collaborator, if necessary.

**June 14-July 14 2013:** The work during the second month will be focused on fine-tuning the model. These weeks will be dedicated to putting the final touches on the model and to perform numerical simulations to examine treatment strategies as mentioned in the summary and the narrative. The preparation of a manuscript for publication will begin once significant results are obtained.