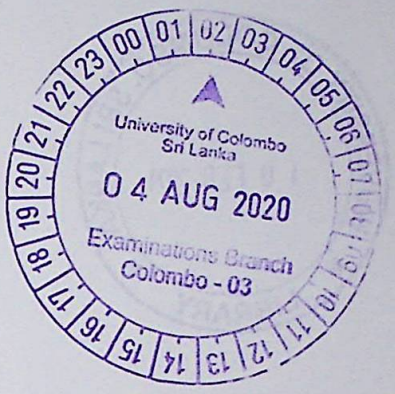

Mathematical Modeling for dynamics of dengue virus-A systems approach

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Abstract

Dengue is a globally important vector-borne virus that causes a spectrum of diseases ranging from symptomatic dengue fever (DF) which causes flu like symptoms to more severe dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). There is an urgent need for a drug or vaccine against dengue, yet none are presently available. Despite considerable efforts, the development of a successful vaccine has remained elusive. Multiple factors have hindered the development of a successful vaccine. One such factor complicating the vaccine development has been the poor understanding of the immune mechanism that is driving virus control during an infection.

In this context, it is important to understand the biological mechanism that is involved during an infection. Mathematical modeling of the underlying biological interactions is a powerful tool in the understanding of immune response during an infection. In addition it has proven to be a valuable tool in providing insights into viral kinetics and disease outcomes. Thus the main objective of this study is to understand the dynamics of virus replication and immune response interaction during a dengue infection using mathematical modeling. For this we analyze different models with different immune components and finally compare the outcomes of these models with experimental results.

Since antibodies are thought to play a dominant role in clearing dengue virus, we first analyzed a mathematical model with antibody immune response where the delay in antibody production was introduced through a Heaviside step function. Since it is not realistic to use a discrete function, we then modeled this delay using a continuous function and analyzed the virus dynamics. It was noted that the viral load declined to negligible levels within 7-14 days as observed in clinical literature. We next coupled antibody immune response with innate immune response. In the simulation model we observed bimodal virus titer peaks. We then added cytotoxic T lymphocytes (CTL) mediated immune response

to this model which generated only one virus titer peak. Our theoretical results are in line with clinical observations.

We then qualitatively validated the simulation results using a data-set that consists of individual dengue viral load data along with antibody data that was made publicly available from a clinical study in Ho Chi Minh City, Vietnam. This dataset includes viral titer data, IgG and IgM antibody data of 60 patients measured over 5 days 12 hours apart. The data was analyzed and was grouped according to different viral titer patterns observed. Three main viral clusters were identified with two peaks, one peak and two peaks with the second peak higher than the first peak. These clustering patterns correspond to the simulation results obtained from different immune response models. Thus we conclude that our simulation results qualitatively fit the experimental results.