Modeling Infectious Disease in Healthcare Problems for the Medical Systems Improvement in Bangladesh

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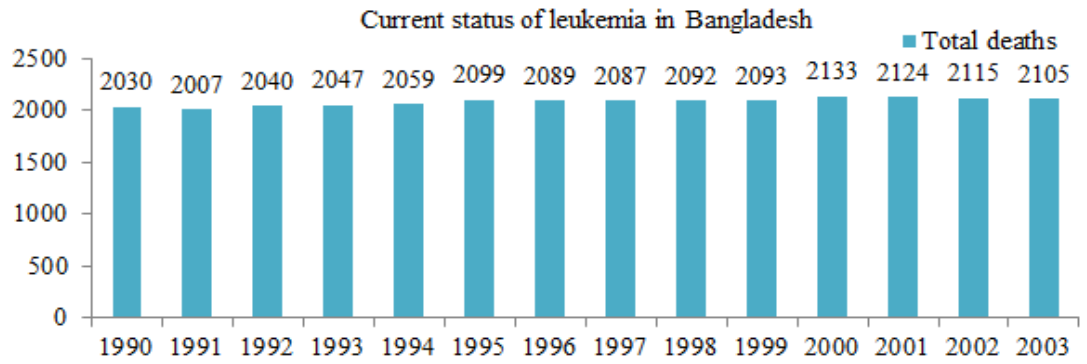
Abstract

Providing proper healthcare to the growing population in Bangladesh has become major concern because of the increasing threats of infectious diseases and their rate of mortality. It has been challenging for the healthcare providers to provide optimal treatment of emerging infectious diseases. In recent years, mathematical models have become important tools in analyzing and describing the changing dynamics of healthcare and biomedical systems. The processes in biology and medicine can be, in general, described by mathematical models where the nonlinear ordinary differential equations are the key ingredients. Optimal control technique fuels on such analysis in obtaining the optimal control strategies. This technique provides new results by applying the old theories. In this paper, we address some recent developments of modeling the nonlinear behavior of immunotherapeutic treatment of leukemia using Adoptive T cell. Optimal control technique can be of advantageous to obtain the better strategy as a special feature in some cases. Numerical treatment is performed to illustrate the results.

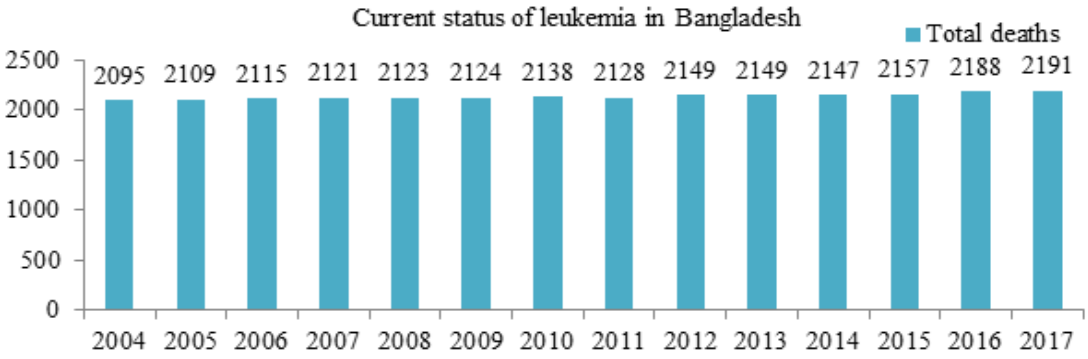
Keywords: Optimal control, Mathematical modeling, Healthcare systems, Numerical simulations.

1. Introduction

Bangladesh has been the most risky geographic distribution for several chronic and infectious diseases like cancer and other fatal diseases. Cancer is a group of disease complications which are mainly characterized by the uncontrolled growth and proliferation of cells in the human body. Leukemia is a horrible type of cancer. It is a malignant cancer of the blood. It is a most common type of cancer in children. Basically, leukemia disease occurs for the uncontrolled growth of abnormal and immature white blood cells (or immune cells) in the human body. In 2009-2013, leukemia was the fifth most common cause of cancer deaths in men and the sixth most common in women. In 2015, approximately 2.3 million people were affected by leukemia and about 353,500 people died from it globally. Leukemia is one of the top most cancers in the world and a very serious blood cancer. Because the symptoms of leukemia often go unexplored and this makes the disease even deadlier. Actually, leukemia is a worldwide curse. There is no such country where leukemia disease does not exist. The first case of leukemia was detected in the 19th century by the European physician and named by a German politician in 1847. Since then, it has been enhanced considerably. It has become a common phenomenon today that to have a cancer patient in every family in Bangladesh. A graphical representation of leukemia related death of Bangladesh from 1990 to 2017 [25] is shown in Figure 1. From Figure 1 we see that in 1990, the number of leukemia related death was 241630. However, the number of leukemia related death is increasing day by day. Here we show a graphical representation of leukemia related death of Bangladesh from 1990 to 2017. It shows that in the 21th century leukemia related death rate has considerably increased worldwide. Leukemia is a type of cancer that affects the blood and bone marrow. The immune system is known to play an important role in the dynamics of leukemia which is the motivation for the work in this paper.



(a)



(b)

Figure 1. (a) Number of leukemia related death from 1990 to 2003; (b) Number of leukemia related death from 2004 to 2017.

There is an extensive body of work which develops models of this type for the treatment of cancer with immunotherapy [(17, 22, and 23)]. Several diseases with immune system response have been modeled as well [(4, 8, 24, and 27)]. We refer readers to [(14, 15, 18 and the references within)] for more detail on leukemia as well as some recent developments. In this paper, we address some recent developments of modeling the nonlinear behavior of immunotherapeutic treatment of leukemia using Adoptive T cell. Our model consists of four nonlinear ordinary differential equations. Our analysis reveals that external re-infusion of immune cells reduces the concentration of cancer cells and infected cells in the blood.

2. What is leukemia?

Leukemia was 1st observed by the European physicians in the 19th century and that time they called the disease "weisses blut," meaning "white blood". Now the word "leukemia" that is used comes from the Greek words "leukos" and "heima" also meaning "white blood". Bone marrow (soft, spongy center of the bone) produces red blood cells, white blood cells and platelets. Red blood cells carry oxygen to cells throughout the body but if there are too few red blood cells, symptoms such as anemia and shortness of breath appear. White blood cells fight against infection. Platelets control blood clotting and also prevent hemorrhaging. The spleen and the lymph nodes produce a type of white blood cell called lymphocyte. Basically, lymphocytes produce antibodies that act against infection and contribute to the body's own immune system. All these blood forming tissues daily release millions of each type of cell into one of the body's two circulatory systems-the blood vessel system and the lymph system. When leukemia strikes, millions of abnormal and immature white blood cells called leukocytes are released into these blood circulatory systems and the abnormal cells slip past this defense system.

3. On Leukemia Treatment

Very recently a tremendous success for leukemia treatments called 'adoptive T cell therapy' has been claimed by the researchers at the University of Pennsylvania which is a milestone towards the immunotherapeutic treatments of leukemia. They showed that two of the three patients after receiving doses of the CAR T cells (chimeric antigen receptor T cells) remained cancer free for more than a year and the findings 1st published in [13]. In several experiment,

researchers showed in their research that all signs of cancer disappeared (a complete response) in 27 of the 30 patients treated in the study. In 2017, two CAR T cell therapies (also known as adoptive T cell therapy) were approved by the United States Food and Drug Administration from which one for the treatment of children with acute lymphoblastic leukemia (ALL) and the other for adults with advanced lymphomas. Our immune system works to recognize and destroy abnormal, immature and mutated cells. But the abnormal and immature cells that eventually become cancer are the ones that slip past this defense system. The idea behind this adoptive T cell therapy is to make immune cells sensitive to cancer-specific abnormalities so that cancer cells can be recognized and attacked throughout the body.
In adaptive T cell therapy, the researchers first collect T cells (a type of immune cells) from the patient's own blood which takes about four hours. After collection, the T cells are genetically engineered to produce special receptors on their surface which are called chimeric antigen receptors (CARs). CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells. These engineered CAR T cells (chimeric antigen receptor T cells) are then grown in the laboratory until they numbered in the billions. Then the expanded population of CAR T cells is infused into the patient. After the infusion, the T cells are multiplied in the patient's body and with the guidance from their engineered receptors; the T cells recognize and kill cancer cells that harbor the antigen on their surfaces. They even produce dormant memory T cells that may spring back to life if the cancer relapses.

4. Mathematical Model of Leukemia

Mathematical models have been used to analyze the dynamics of chronic diseases like leukemia over the years. To model leukemia, we first need to consider the spread of leukemia in the blood circulatory system. Our interest is to present a mathematical model of leukemia and analyze that how change happened in the blood cells after using adoptive T cell. In this paper, we present a four compartmental model of leukemia which has been taken from [2]. Some amount of infected cells also losses due to interaction with cancer cells. So we have modified this model taking a decay rate parameter β_1 of infected cells whose value is taken from [19]. Taking parameter β_1, we get considerably better result which is shown in our numerical simulations. Let S be the population of susceptible blood cells in the circulatory blood, I be the population of infected blood cells, C be the population of leukemic cells (abnormal cells), W be the population of white blood cells or immune cells in the body. The population of susceptible blood cells starts with a source term A into the circulatory blood from compartments like bone marrow, lymph nodes and thymus. Parameters a_0, β_0, k_0 and b_0 are the natural death rate of susceptible blood cells, infected cells, cancer cells and immune cells respectively. The parameter β is the loss rate constant of susceptible blood cells because of being infected by the cancer cells. Parameter k_1, which represents the loss rate constant of cancer cells due to interaction with immune cells. Some immune cells will also be decayed due to the presents of leukemic cells or cancer cells in the blood which can be denoted by b_1. B is the rate of external infusion of T cells or immune cells into the cancer patients. If cancer relapses, the immune cells will be proliferated at a constant rate b. The transfer diagram of the model is shown in Figure 2.

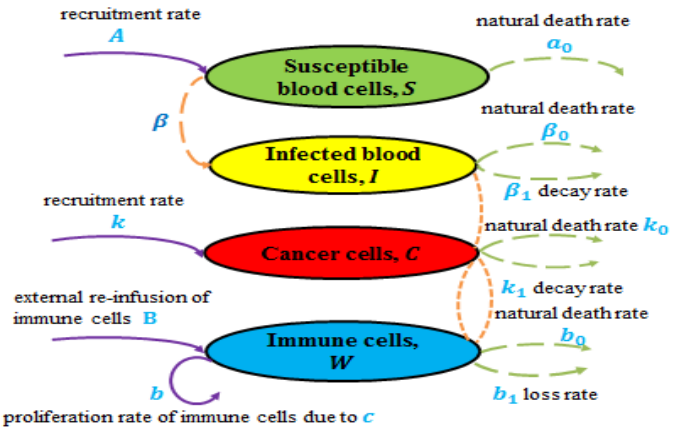


Figure 2. Cell population diagram of leukemia. In this figure, dotted lines without arrows represent interaction terms among the compartments.

Our modified model is governed by the following system of ordinary differential equations:

$$\frac{dS}{dt} = A - a_0 S - \beta SC \tag{1}$$

$$\frac{dI}{dt} = \beta SC - \beta_0 I - \beta_1 CI \quad (2)$$

$$\frac{dC}{dt} = k - k_0 C - k_1 CW \quad (3)$$

$$\frac{dW}{dt} = B + bC - b_0 W - b_1 WC \quad (4)$$

The solutions of the model (1)-(4) are bounded within the region

$$\Omega = \left\{ (S, I, C, W) : 0 < S(t) \le \frac{A}{a_0}, 0 < S(t) + I(t) \le \frac{A}{\eta}, 0 < C(t) \le \frac{k}{k_0} \text{ and } 0 < W(t) \le (B + \frac{bk}{k_0}) / b_0 \right\} \text{ and } \eta = \min(a_0, \beta_0)$$

We have determined the basic reproduction number R_0 which can be defined as the average number of secondary infections produced by one primary infection in a wholly susceptible population. Finding the basic reproduction number R_0, we may observe the endemic result of disease in populations. If $R_0 > 1$, the endemic disease will persist but if $R_0 < 1$, the disease will die out. If $R_0 = 1$, the disease will be constant. Here the basic reproduction ratio of the model (1)-(4) is $R_0 = (\beta S) / (\beta_0 + \beta_1)$. Considering all the values of parameters (taken from [2] and [19]), we see that the value of R_0 is less than 1. So the epidemic disease will die out gradually for using immunotherapy.

5. Numerical Simulations

We perform numerical simulations of our model proposed in (1)-(4) by the *ODE-solver* using MATLAB programming. To solve the epidemic model (1)-(4), we consider the initial values as $S(0) = 149.079$, $I(0) = 1.082$, $C(0) = 1.5971$, $W(0) = 252.26$ and all the values of the parameters as ($A = 1.5$, $a_0 = 0.01$, $\beta = 0.00005$, $\beta_0 = 0.003$, $\beta_1 = 0.005$, $k = 10$, $k_0 = 5$, $k_1 = 0.005$, $B = 15$, $b = 0.01$, $b_0 = 0.05$, and $b_1 = 0.001$) are taken from [(2, 19)]. The result of the simulations of individual classes in the absence of immunotherapy is presented in Figure 3. Also we run the program with the presence of immunotherapy and the result is shown in Figure 4. We perform simulations for the time 200 days. We solve the model (1)-(4) for different values of the parameter k taking all other values same and the simulation of cancer cells is shown in Figure 5. Now we run the simulations of the epidemic model (1)-(4) for different values of parameter B with all other parameters same as before and the simulation of cancer cells is presented in Figure 6. Again, we run the simulations for different stimulation rate or antigenicity rate b of immune cells and the simulation of cancer cells is shown in Figure 7.

From Figure 3, it is easy to observe that at the very beginning of leukemia infections, when any form of immunotherapy as 'adoptive T cell' is not initiated for treatment, the number of susceptible cells and immune cells are decreasing quickly over time and at the same time the other cells (such as infected and cancer) are increasing very fast. We can see from Figure 4 that when the immunotherapy is fully effective, number of susceptible cells and immune cells increase over time while the others cells (such as infected and cancer) decrease. From Figure 5, we observe that cancer cells increase as the cancer recruitment rate increases in the blood whereas Figure 6 shows that cancer cells decrease as the external re-infusion rate of immune cells due to immunotherapy increases in the blood. Again from Figure 7 we see that cancer cells also decrease as the proliferation rate of immune cells increases in the patient's body.

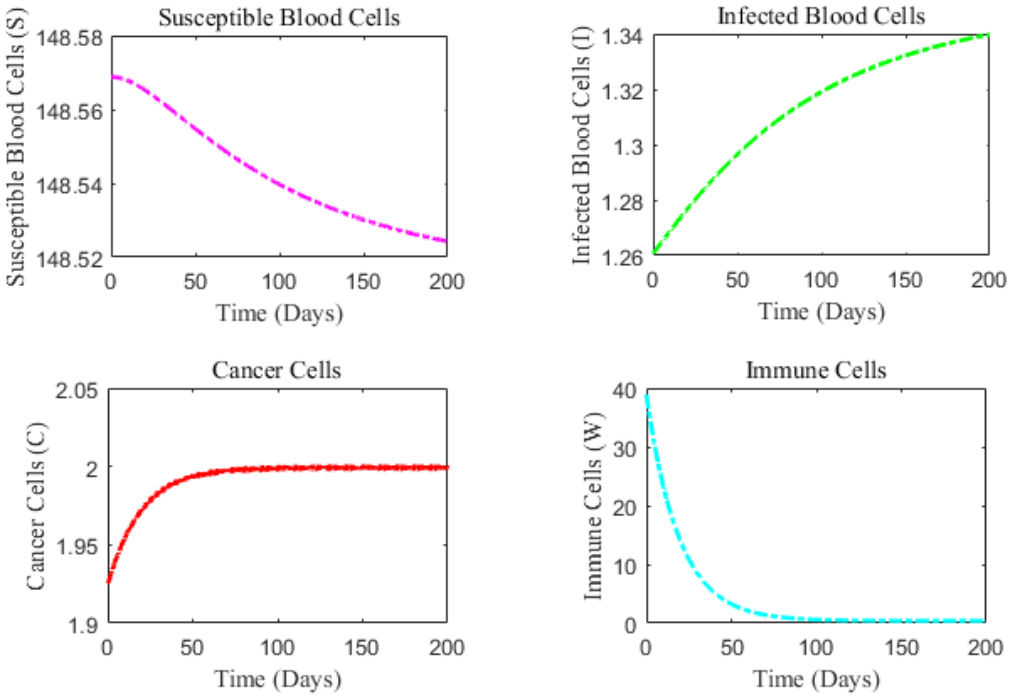


Figure 3. State trajectories in absence of immunotherapy (i.e. $B = 0$). We observe that the number of susceptible blood cells and immune cells are decreasing wheres the number infected cells as well as cancer cells are increasing very fast over the time.

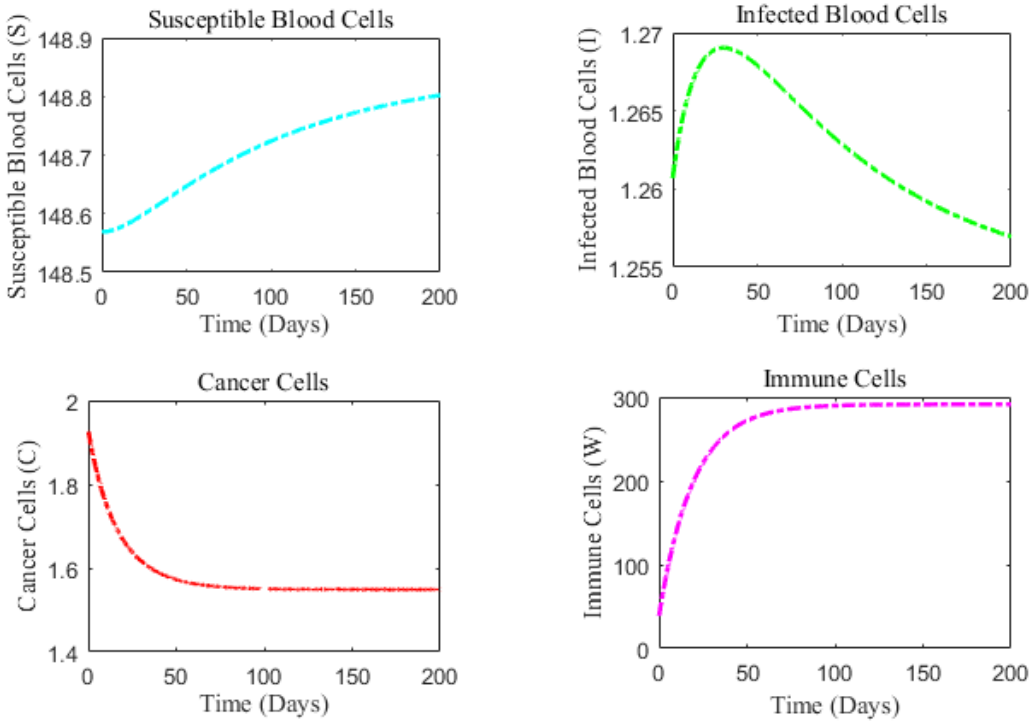


Figure 4. State trajectories with the presence of immunotherapy (i.e. $B = 15$). We observe that the number of susceptible blood cells and immune cells are increasing wheres the number of infected cells are initially increasing but gradually decreasing as well as cancer cells are decreasing very fast over the time.

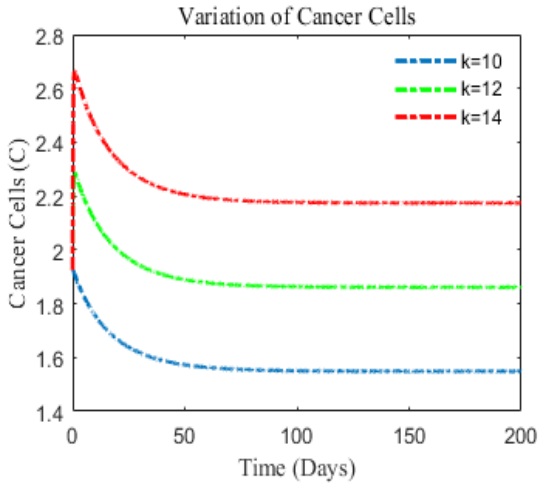


Figure 5. Variation of infected cells for different growth rate k of cancer cells. We observe that the number of cancer cells increases as the cancer recruitment rate k increases in the body.

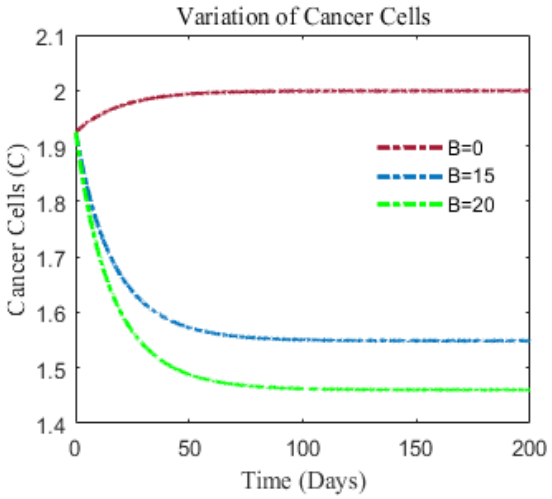


Figure 6. Variation of cancer cells for different growth rate B of external re-infusion of immune cells. We see that the number of cancer cells decreases as the external re-infusion rate B increases in the blood.

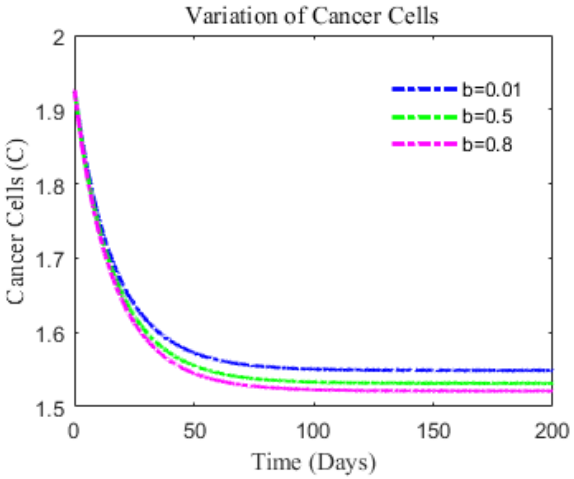


Figure 7. Variation of cancer cells for different stimulation rate or antigenicity rate b of immune response due to cancer antigen present in the blood.

6. Conclusions

Bangladesh is the most densely populated (75% in rural areas) country in the world and the total population is its manpower. So the ultimate demand is to take immediate necessary steps/treatment so that the leukemia infections can be cured completely. This paper focuses on the fundamental scenarios of leukemia and the nonlinear behavior of immunotherapeutic treatment by using adoptive T cell. A four compartmental model for leukemia has been formulated mathematically and then analyzed numerically. The analysis of the mathematical model and the simulation predictions clarify the mechanisms of the disease propagations and cancer cell interactions in the human body and thus suggest treatment strategies that could be implemented to defend the disease. Since proper medications as well as effective vaccine are still not available for the treatments, this study may help the doctors and biologists for determining and obtaining preventive strategies from this deadly disease leukemia.

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