Numerical simulations of cancer treatment prediction: modeling the influence of immunity

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Abstract
Malignant tumors, also called cancer or malignant neoplasms, are life-threatening tumors that invade the borders of other tissues or spread to other parts of the body and grow in various locations [1]. Recent evidence suggests that cancer cells generated by genetic mutations are eliminated by immune cells. Immune cells are immune cells that recognize and attack foreign substances, pathogens, and cancers in the body. A decline in immunity due to ageing or nutritional deficiencies, or due to immunosuppression is associated with increased risk of cancer cells [2]. Immunotherapy is a treatment method that activates the body's innate immune function to eliminate cancer cells. This study, therefore, set out to assess the effect of immunotherapy using numerical simulations. Parameters, such as the conditions of cancer cell death with immune cells, cell division, and angiogenesis, were theoretically set and introduced into the model.

Keywords: Cancer, Immunotherapy, Immune cell, Numerical simulation

1. Introduction
Malignant neoplasms have been thought of as a key factor in causing death. The issue of malignancies has received considerable critical attention. Recently, there has been renewed interest in FY2016. Researchers have shown an increased interest in cancer predictions with various conditions and treatment effects using numerical simulations to support the diagnoses and treatment methods of cancer [3]. The specific objective of this study was to examine the immunotherapy method as one of the cancer treatment methods. The present research explores, for the first time, the effects of the method of cancer treatments that use anticancer drugs or radiation. This treatment has proved to be useful because it has fewer side effects. After all, the patient is treated with their immune cells. Immunotherapy is expected to become increasingly widespread in the future [4]. There is still uncertainty, however, whether what kind of patients it is effective for and how long to beat the dose. The purpose of this investigation is to explore the effect of immunotherapy by numerical simulations using the particle method. Apart from the model of FY2016, we have made the model more like a real-world phenomenon by improving the accuracy of immune cell distribution and introducing nutrient-deficient cancer cell death. The results are expected to contribute to clinical research on cancer treatments and explanatory materials for cancer patients.
2. Computational Models and Analysis Targets

The analytical model is based on a particle method [5] that has previously been used for numerical simulations of tumor growth and angiogenesis. The particle method is a method for computing the behavior of a continuum by the motion of a finite number of particles. Each particle can be treated as a particle that moves around the calculation point while maintaining variables such as nutrient content and pressure. This analysis deals with cancer cell particles, vascular cell particles, and immune cell particles. Immune cell particles are placed on vascular and cancer shape data generated from cancer images and changes in cancer cell particles are observed. The cancer images used and the images processed and modeled from them are shown in Figure 1. The image in Figure 1a is binarized, and when the shading value difference is 0.4, it is recognized as cancer. The particles placed at the recognized location as cancer are free particles. The image area is 75 mm wide and 75 mm high.

![Cancer imaging and vascular placement](image)

**Figure 1.** Physical model used in the analysis.

In this study, we focused on immune cells that recognize and attack foreign substances, pathogens, and cancers in the body. Immunotherapy is a method of treatment in which immune cells are activated outside the body and then returned to the body to attack cancer cells [6]. In this study, we compare changes in the tumors by predicting cancer growth in the absence of immunity, predicting the effects of the body’s natural immunity, and predicting the therapeutic effects of immunotherapy.

For a tumor to grow, blood vessels need to be pulled into the tumor. If blood vessels cannot be pulled into the tumor, the lack of nutrients will cause the cancer cells in the tumor to suffocate or become malnourished. Accordingly, many cancer cells produce factors that promote angiogenesis [7]. These factors help the newly formed blood vessels feed the tumor and ensure that the cancer cells can continue to divide. Here, the nutrient diffusion equation between cells is shown in equation (1), where \( C \) is the amount of nutrients, \( D \) is the diffusion coefficient, and \( \alpha \) is the nutrient consumption coefficient.

\[
\frac{\partial C}{\partial t} = D \left( \frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2} \right) - \alpha \tag{1}
\]

The nutrient content of the particle of interest is given by equation (2), where \( i \) is the particle of interest and \( j \) is the target particle. \( X \) is the distance between particles. If the nutrients in the vascular cell particles are set to 1, the nutrient diffusion distance to the cancer cell particles is 200 \( \mu \)m. Set the value of \( \alpha D \) that satisfies this condition. In this case, we set it to 0.1.

\[
C_i = \frac{\sum_{j} \frac{C_j}{X_{ij}^2} \cdot \frac{\alpha}{D}}{\sum_{j} \frac{1}{X_{ij}^2}} \tag{2}
\]
The division of cancer cell clusters depends on the nutrient concentration within the cluster. Cancer cells with high nutrient concentrations actively divide, while nutrient-depleted cancer cells die or become dormant over time. The equation for the cell division time [8] is shown in equation (3), where $T$ is cell division time, $T_{\text{min}}$ is the shortest cell division time, $Kc$ is the relaxation coefficient of the trophic term, and $C$ is the amount of nutrient concentration. The shortest cell division time was 30 days, and the relaxation coefficient of the trophic term was 0.5.

$$T = \frac{T_{\text{min}}}{1 + Kc \left( 1 + \frac{Kc}{C^2} \right)}$$

(3)

3. Analysis Conditions

Effective immune cells have difficulty penetrating tumors and can only be present in approximately 20% of a tumor as transported by the blood vessels. Therefore, in the simulations, 20% of the immune cells outside the tumor were placed inside the tumor. Cancer cells were killed by the immune cells at a rate of 1% per hour. During that time, an immune cell could attack the nearest cancer cell within a range of two particles surrounding the immune cell.

Immunotherapy results in the body having approximately 10 times the normal number of immune cells [6]. In actual immunotherapy, the cytotoxic activity of the immune cells falls below the effective range in 3–4 days; therefore, new immune cells are injected in a 3–4-day cycle [9]. In this analysis, this process was represented by the probabilistic annihilation of the immune cells and their re-emergence every 4 days.

The amount of nutrients in the blood vessels, which serve as the nutrient source of the cancer cells, was set to 1; the nutrients then diffused to the surrounding particles. However, it is difficult for nutrients to reach blood vessels that are in areas of high pressure inside a tumor. Therefore, coupled with the tumor pressure distribution [3] shown in Figure 2, the nutrient content of the blood vessel cells with pressure values of 20 or more was assumed to be the value resulting from diffusion from the surrounding cells. The distribution of the nutrients is presented in Figure 3.

Figure 2. Pressure distribution in the modeled tumor.
Malnourished cancer cells may take months to die. To represent this in the model, cells with nutrient levels below 0.42 were eliminated over an average of approximately two months.

4. Analysis Results
As can be seen from Figure 4 below, the 30-day cancer particle count predictions in the absence of immunity, with natural immunity, and with immunotherapy.

4.1 Prediction in the absence of immunity
The purpose of this section was to provide result of the analysis of only cancer cell particles and vascular cell particles, without the placement of immune particles. As can be seen from the green triangles in Figure 4 above, the cancer growth can be represented in the case of the absence of an immune attack. Introducing cancer cell death in nutrient-deficient areas and modifying the nutrient content of the high-pressure blood vessels improved the model behavior compared to the rapid cancer growth seen in previous models [3].

4.2 Predicting the effect of natural immunity
This is the result of the analysis of the placement of immune cell particles. It can be seen from the data of the blue diamonds in Figure 4 that the number of cancer cells in the case of natural immune cells is lower than in the case of no immunity, representing the attack by immune cells on cancer cells. However,
natural immunity alone is not effective in curing terminal cancers, and we can see that the number of cancer cells is increasing.

4.3 Predicting the effect of immunotherapy
The results obtained from the preliminary analysis of modeled immunotherapy by placing about 10 times as many immune cell particles as natural immunity, and making immune are set out in Figure 4. We can see that the cells disappear stochastically and reappear every 4 days. The red squares in Figure from the Figure 4 above we can see that the cancer cells are attacked and killed by periodically administered immune cells. The results indicated that the number of cancer particles was only reduced in the case of immunotherapy, which represents the treatment effect of immunotherapy. The results of an analysis of the cancer model with immunotherapy are provided in Figure 5. Figures 5a–5d compare the effects of immunotherapy on days 1, 10, 20, and 30, respectively. It is apparent from this figure that the cancer cells in the malnourished areas are gradually killed and the tumor shrinks (see Figure 5). In the same vein, regression of the blood vessels can be confirmed in response to the death of the cancer particles.

![Figure 5](image-url)

**Figure 5.** Modeled results of immunotherapy for days (a) 1, (b) 10, (c) 20, and (d) 30.

5. Conclusion
The present study was designed to improve the placement of the immune cells and the nutrient content of high-pressure blood vessels and to introduce the death of cancer particles in nutrient-deficient areas.
Hence, we were able to model the effect of immunity on cancer cells in a manner closer to the real phenomenon compared to conventional cancer models.

In the prediction without immunity, the current data highlight the importance of simulating a cancer model with only cancer cells and blood vessels with an appearance of the cancer growth. These findings also suggested a prediction of the effect of natural immunity so that the immune cells can suppress the cancer growth when compared to the prediction without immunity. Therefore, the attack on the cancer cells by the immune cells could be expressed. The prediction of the effect of immunotherapy revealed that the cancer cells were killed in the presence of periodic infusions of immune cells. The treatment effect could be observed as the tumor shrank over time.

Acknowledgments
We have received support and advice from many people in advancing this research, and we have successfully completed the paper. Dr. Ichiro Miura of Juntendo University and Dr. Sae Saito of Tohoku University gave us medical knowledge, images, experimental data, and guidance on our research, and we were able to proceed with our research in a favorable environment. We would like to thank you for this opportunity. Prof. Katsuya Nagayama has been paying close attention to our progress and has helped us to deepen our understanding of our research. We hereby express my gratitude.

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