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Numerical modelling of the influence of stromal cells on tumor growth and angiogenesis

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Abstract. According to the statistics provided by the Ministry of Health, Labor and Welfare the death of one in 3.5 Japanese people is attributed to tumor highlighting the need for active research on malignant tumors. Early detection can be cited as a countermeasure against malignant tumors, but it is often difficult to observe the growth process, and thorough understanding of the phenomena will aid in more efficient detection of such tumors. A malnourished benign tumor may create new blood vessels from existing ones and proliferate abnormally by absorbing nutrients from these newly created blood vessels to become malignant. Different factors influence the shape of tumors and shape is an important factor in evaluating their malignancy. Because interstitial cells greatly influence tumor growth, investigating the influence of stromal cells on tumor growth will help in developing a better understanding of the phenomenon.

1. Introduction

The study of malignant tumors has garnered much attention globally owing to the high mortality rates associated with them. Statistics provided by the Ministry of Health, Labor and Welfare indicate that the deaths of one in 3.5 Japanese people can be attributed to tumors of various types. A malnourished benign tumor may create new blood vessels from the existing ones and proliferate abnormally by absorbing nutrients from these newly created blood vessels to become malignant. Early detection is often cited as a countermeasure against malignant tumors [1], but a lack of clear understanding of the phenomena makes it is difficult to detect and observe their growth. Different factors influence the shape of tumors, and shape is an important factor in evaluating their malignancy. This work studies malignant tumors and the related angiogenesis using numerical analysis based on a particle model [2, 3]. In this method, calculation points or points under active consideration are assumed to move across the mass while storing relevant quantities at mass points. One particle is represented as one cell. Because the shape is maintained by balancing between particles, the direction of cell division and migration is not limited.

Stromal cells such as fibroblasts are distributed around the cancer cells as shown in figure 1. Stromal cells have great influence on tumor growth as shown in figure 2. However, thus far, we have performed tumor growth analysis without introducing stromal cells. Therefore, by introducing stromal cells into analysis, we investigate the influence of stromal cells and use it to elucidate the phenomenon of tumor growth.

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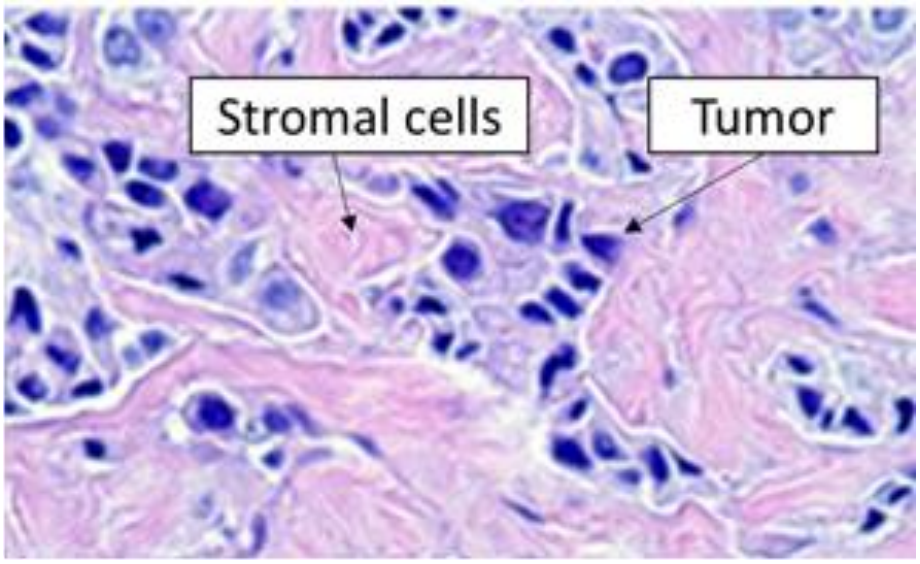

Figure 1. Distribution of stromal cells and fibroblasts in invasive breast cancer in humans.

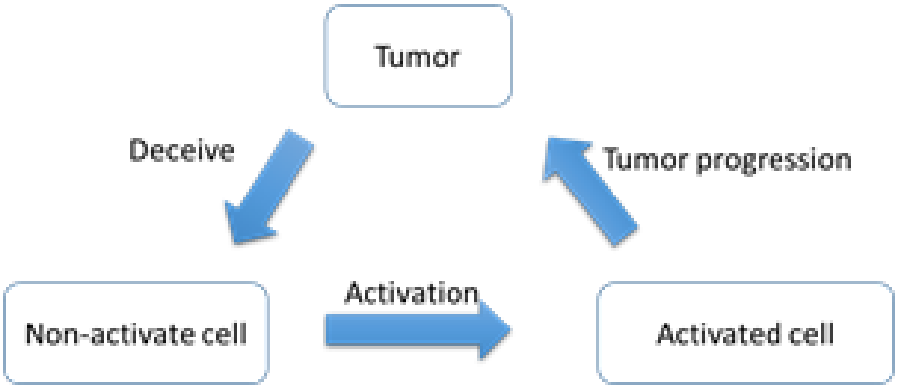

Figure 2. Relation between stromal and tumor, artery.

2. Calculation Model

For analysis, particles are first placed in a 2D region, and cancer cell group particles representing blood vessels are arranged around this region. In the next step, the amount of nutrient diffusion between the blood vessel and the cell is calculated. Equation (1) represents diffusion in cells taking into account the nutrient consumption. The left-hand side of equation (1) represents the temporal variation of the quantity of nutrition, C. The diffusion coefficient is represented by D, whereas α is the nutrient consumption coefficient.

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

The time required for a cancer cell to divide is dependent on the availability of nutrients to that cell. Cancer cells with access to high nutrient concentrations divide actively while the group of cells with reduced nutrient concentration becomes dormant. The cell division time T can be obtained from equation (2). In this equation, T_{min} represents the shortest cell division time, Kc is the relaxation coefficient of the nutrition term, and C is the nutrient concentration.

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

Stromal cells are modelled as particles that can proliferate, migrate, etc. The nutrient consumption or diffusion and the frequency of cell division in stromal cells are modelled similar to that in cancer group cells. In stromal cells, the nutrient consumption coefficient α is set to 0.1 and the shortest time for cell division is taken as ten times as that for cancer group cells. Thus, for stromal cell particles, equation (1) and equation (2) are modified to equation (3) and equation (4) respectively.

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right) - 0.1\alpha \quad (3)$$

$$T = \frac{10T_{min}}{1+Kc}\left(1 + \frac{Kc}{C^2}\right) \quad (4)$$

Figure 3 represents the flow of calculation in the analytical model.

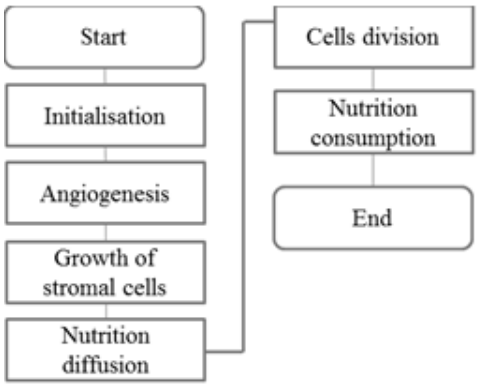

Figure 3. Flowchart showing steps in the analysis of stromal cell growth using a particle-based method.

3. Analysis Condition

First, a 2D analysis of tumor growth in the early stages of development was performed figure 4 shows the initial condition, where a single cancer cell particle was placed alongside one among 16 blood vessel particles (artery) in the region of analysis. The minimum vessel diameter was set to an initial value of 50 μm. In addition, the nutrient diffusion distance by the blood vessel was set to 200 μm. The size of one cancer cell group particle was set to be 50 μm and the minimum cell division cycle was 18 hours. Stromal cells may be supplied from blood vessels or may be pre-existing [4]. Therefore, analysis was conducted in two cases. In case 1, inactivated stromal cells are generated only in the vicinity of blood vessels, and only pre-existing but inactivated stromal cells around the cancer cells are activated. In case 2, activated stromal cells are generated around cancer cells. For comparison, we also analyzed cases without stromal cells and case 1-2 fused.

The next analysis of early-stage tumor growth and angiogenesis was performed in a three-dimensional region. Figure 5 represents the initial state, where one cancer cell particle was placed in the vicinity of the center of the region where a blood vessel was present. The initial conditions and parameter values were the same as those used in the 2D analysis. Two analysis cases were considered here, the conditions for the occurrence of stroma being the same as those in the 2D analysis.

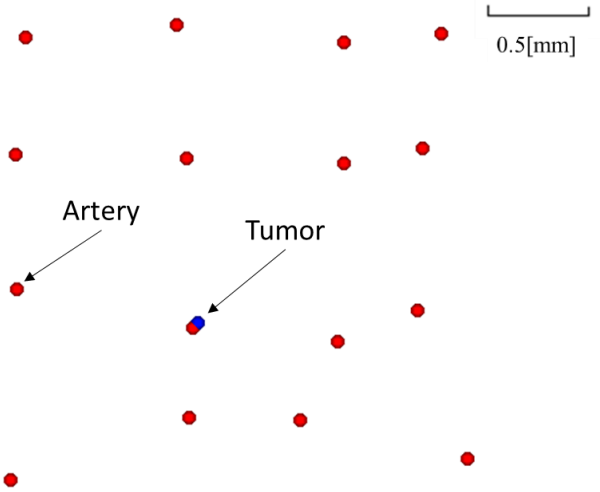

Figure 4. Initial conditions for the 2D modeling of early-stage tumor growth.

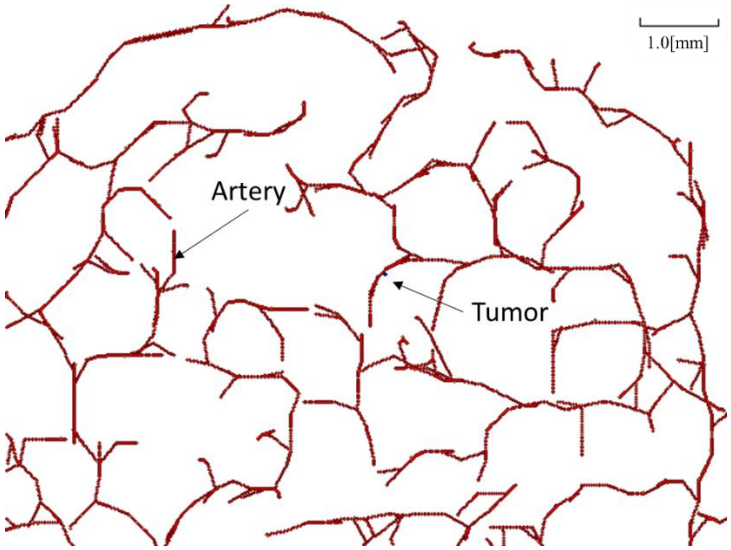

Figure 5. Initial conditions for the three-dimensional modeling of early-stage tumor growth and angiogenesis.

4. Results and Discussion

The influence of stromal cell growth on tumor development and shape was examined in detail using the methods and cases described in earlier sections. Figure 6 shows the distribution of cancer cells and stromal cells for case 1 in which stromal cells were generated only around blood vessels. In this case, the tumor was irregular in shape. This is because the inactive stromal cells around the periphery of the blood vessels push the cancer cells outward, making the tumor boundaries irregular. Figure 7 shows the distribution of cancer cells and stromal cells for case 2 in which stromal cells were generated only from the periphery of the cancer. In this case, the stromal cells were distributed so as to envelop cancer cells. Moreover, the size of the tumor as a whole was smaller than that in case 1. This is because cancer cells consume nutrients at a higher rate than stromal cells and compete with each other for nutrition. Those cells to which nutrients do not reach thus become incapable of division. Figure 8 shows the result of

case without stromal cells. Figure 9 shows the result of case 1-2 fused. When stromal cells were present, the tumor became larger than in the absence of stromal cells.

The results of the three-dimensional analysis are presented in figure 10 and figure 11. The results obtained are similar to the case 2 results in the 2D analysis, where stromal cells cover the tumor. The size of the tumor as a whole became larger than the condition where stromal cells did not develop. This is because the nutrient consumption of stromal cells is smaller than that of cancer cells, and nutrition tends to reach the cancer cells leading to more cell division and consequently, larger tumors. Also, the blood vessels vascularized to cover the entire tumor. This is because the pressure inside the tumor is high, and neovascularization cannot be done.

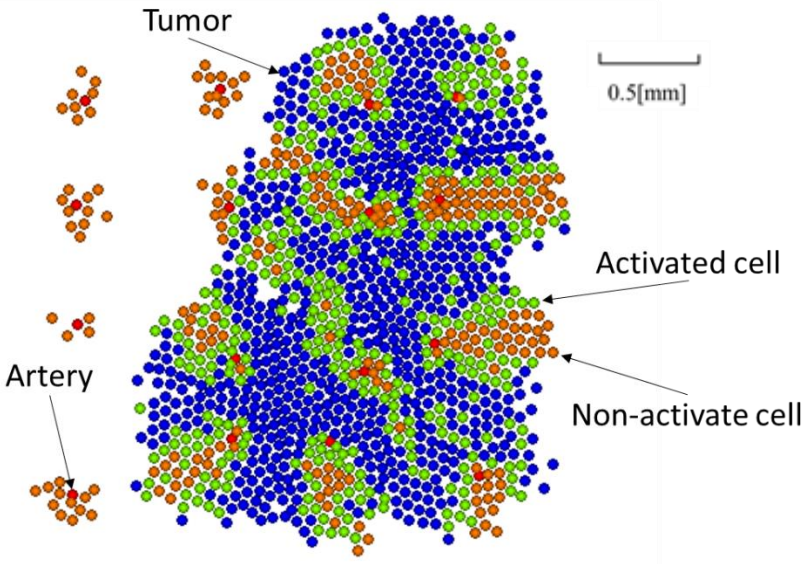

Figure 6. 2D representation of the distribution of cancer cells and stromal cells around arteries in case 1, wherein stromal cells are generated only in the vicinity of blood vessels.

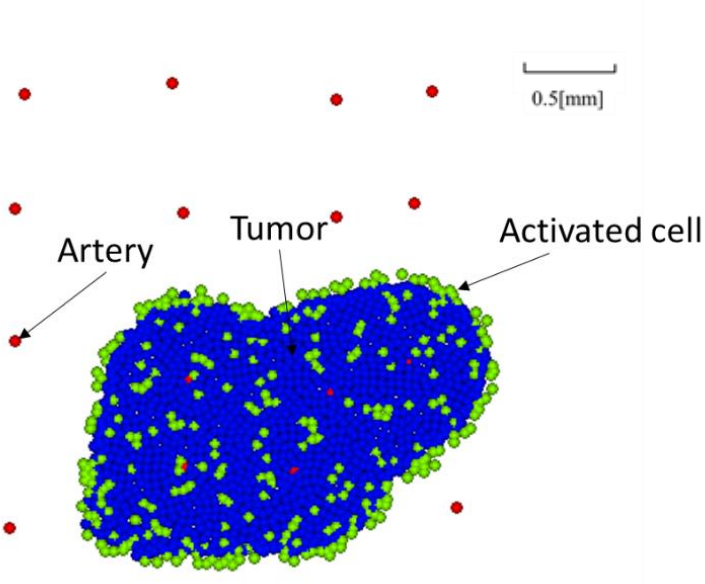

Figure 7. 2D representation of the distribution of cancer cells and stromal cells around the tumor in case 2, where stromal cells are generated only on the periphery of the tumor.

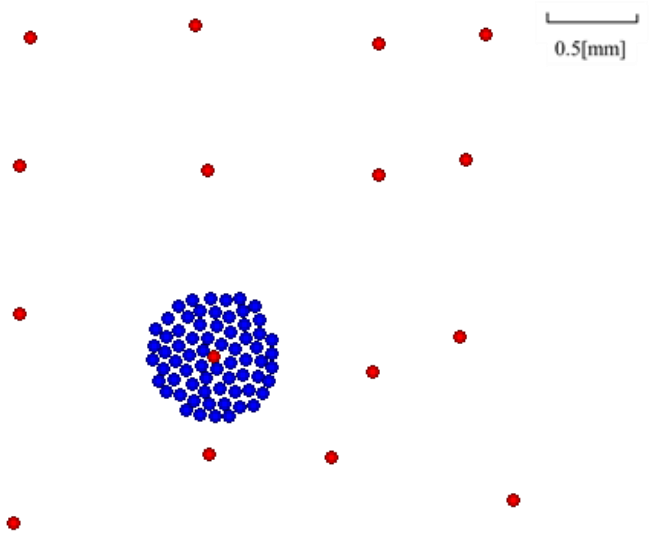

Figure 8. Case without stromal cells.

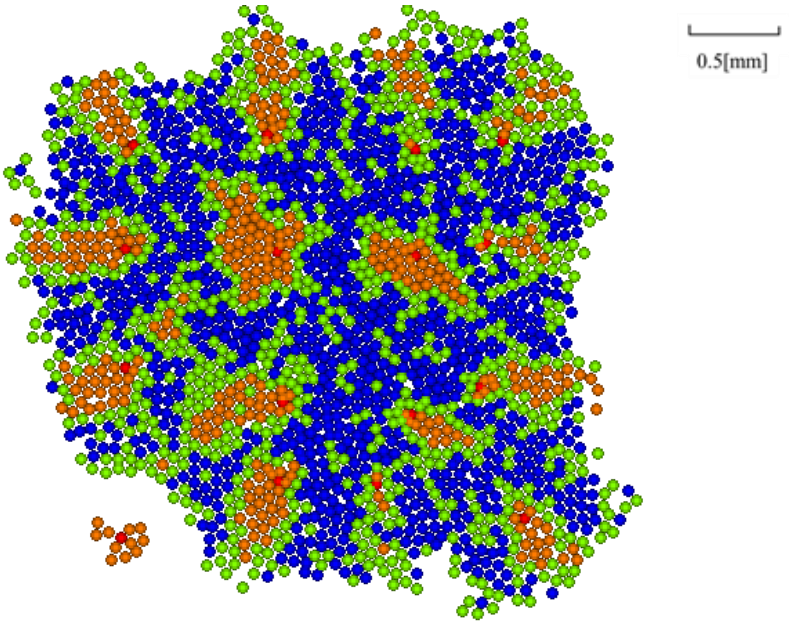

Figure 9. Case 1-2 fused.

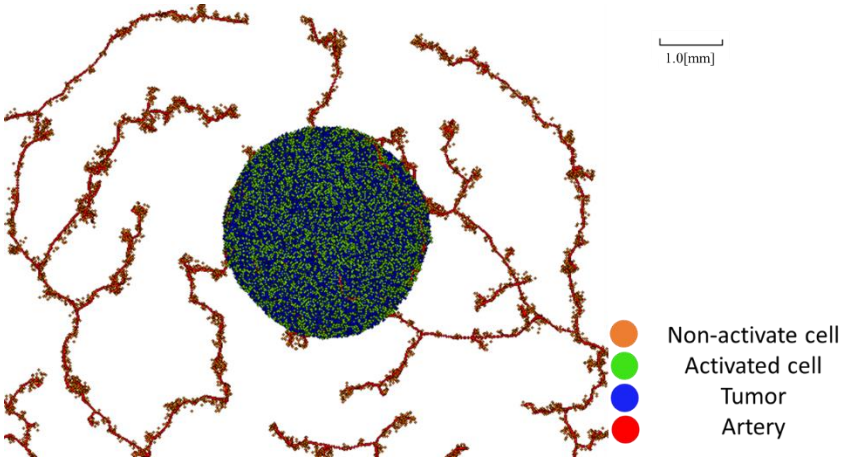

Figure 10. Distribution of stromal cells near the artery and around the tumor in the three-dimensional model

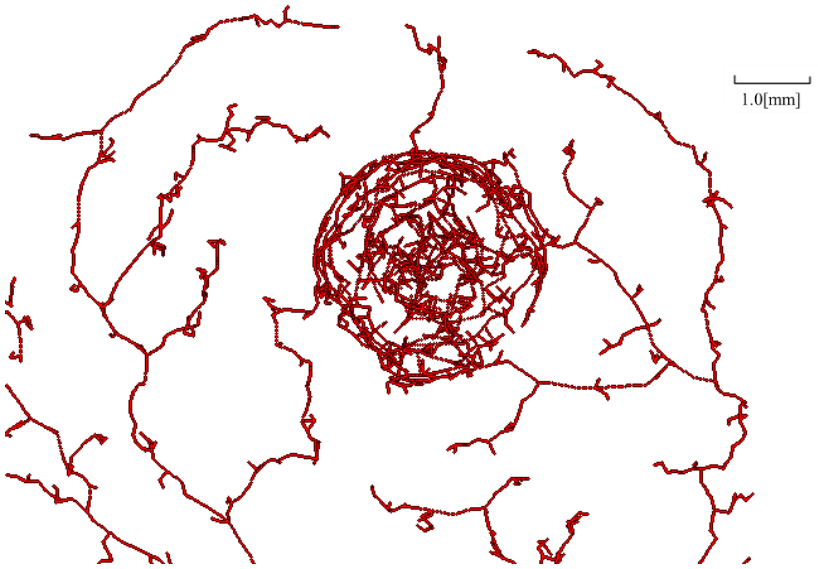

Figure 11. Distribution of newly generated blood vessels in the tumor depicted in the 3D model

5. Conclusion

In this study, we performed a numerical simulation of tumor growth and angiogenesis using a particle model and real images. The shape and size of the malignant tumor changed significantly depending on how the stromal cells were generated. However, the distribution of cancer cells and stromal cells could be approximated to real images, regardless of how stromal cells were generated. A three-dimensional numerical model was also developed, which can effectively predict tumor growth and angiogenesis.

The next steps would be the validation of the model with experimental data and refinement of the existing model so as to make it suitable for predicting the possible malignancy of tumors.

Reference

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