

Mathematical modeling for angiogenesis

By

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Abstract

Angiogenesis is a biological phenomenon in which new vascular networks are constructed from existing blood vessels. In this article, we explain several mathematical models for it proposed by the author and the co-workers. In particular, we explain a simple model of one dimensional dynamical system model, and the two dimensional elliptic and three dimensional ellipsoid particle models. They present unique blood vessel network patterns.

§ 1. Introduction

The top three causes of death in Japan are malignant neoplasms (cancer), cerebrovascular disease and heart disease. All of these are related to vascular anomalies, making the elucidation of the mechanisms of angiogenesis a matter of great medical importance[1, 2]. Especially in cancer, the leading cause of death, it is a challenge to understand the phenomenon of angiogenesis, i.e. the formation of new vascular networks from existing vessels[3]. This is because cancer cells release enzymes such as vascular endothelial growth factor (VEGF), which cause angiogenesis and allow them to grow by obtaining nutrients and oxygen from the newly created blood vessels. Furthermore, cancer cells can migrate through newly created blood vessels into the body, causing cancer metastasis. From the point of view of cancer therapy, a better understanding of the mechanisms of angiogenesis is also of great importance.

In angiogenesis, endothelial cells (ECs) proliferate and move out of existing vessels to form new primitive vessels. Hence, the dynamics of ECs and resulting patterns of blood vessel networks are of primary interest in angiogenesis research. In particular, the

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relationship between the shape of ECs and the pattern formation has been well studied both experimentally and theoretically. Experiments showed that VEGF induces elongated shapes in ECs [4]. Endothelial cells that have not been genetically engineered constitute a network pattern, while ECs blocked VEGF signaling showed a round shape and formed aggregated clusters (Fig. 5 in [4]). Furthermore, in recent in vitro experiments, the dynamics of ECs were observed by time-lapse imaging in detail, and it was found that the ECs exhibit very complex phenomena so called cell-mixing (tip cells are constantly replaced by fast-moving followers that overtake other ECs)[8].

In order to model angiogenesis, taking all the factors into account is practically impossible even in its primary stage of sprouting vessels since angiogenesis consists of very complex multicellular processes. We have to consider individual and heterogenous shapes of ECs, interactions with extracellular materials, variety of chemical and biological reactions, effect of temperature gradient and changes, time delay to the responses, noise and fluctuations from the surroundings, and so on. Hence, we first focused on the effects of the cell-to-cell interaction that we conjecture essential in the cell-mixing phenomenon, elongation and bifurcation, and showed that deterministic two-body interaction between ECs plays an essential role in the cell-mixing effect[9, 10]. Then, we considered the effects of the shape of ECs. For this purpose, we proposed two dimensional ellipse model and three dimensional ellipsoid model, where the oblateness of the ellipse or the ellipsoid is most significant parameter which determines shape of blood vessel network patterns[11, 12, 13]. In the following sections, we review the models and resulting network patterns.

§ 2. Discrete dynamical system model

In vitro experiments with mouse aortas provide the following facts about EC movement in angiogenesis.

- An EC does not move when it is isolated, while it starts moving when another EC comes close to it.
- Bifurcation of blood vessels takes place when the density of ECs at the tip of a vessel becomes high.
- Vessels always bifurcate, never more than three branches.
- The bifurcation angle is approximately 60 degrees.

From the above observation, let us consider sprouting of a blood vessel from the generated blood vessel network that arises from an aortic ring. We discuss the dynamics of ECs with a kind of equation of motion and also describe elongation and bifurcation of the

vessel. We suppose that there is no neogenetic vessel around the aortic ring at the initial time $t = 0$ and a new blood vessel sprouts in a certain direction according to the supply of ECs for $t > 0$. The n th ($n \in \mathbb{Z}_{\geq 0}$) EC comes to the origin of this neogenetic vessel network at time step $t = \sum_{i=1}^n a_i$ with an initial velocity $v_{ini}(n) \geq 0$, where $a_i \in \mathbb{Z}_{>0}$ is the time interval between the incidence of i th EC and that of $(i-1)$ th EC. For the time being, we examine the dynamics of ECs only in the first neogenetic branch, taking into account the effects of two-body interactions between ECs in a branch. Although interactions among ECs are very complicated and have not been well-understood, direct contact between both membranes may be considered to activate chemical channels and increase the mechanical drive of the ECs. For short distance, the interaction force will turn out to be repulsive due to excluded volume effect, while it will turn out to be attractive if the distance becomes larger because of the interaction with pseudopodia. Thus we propose a mathematical model which is given by the discrete time evolution equations:

$$(2.1) \quad x_n^{t+1} = x_n^t + v_n^t$$

$$(2.2) \quad v_n^{t+1} - v_n^t = -\gamma v_n^t + \sum_{k \neq n} F(x_n^t - x_k^t),$$

where $x_n^t \geq 0$ is the position of the n th EC measured from the origin at time step $t \in \mathbb{Z}_{\geq 0}$, the time unit ($\Delta t \equiv 1$) may correspond to the specific response time, the parameter γ ($0 < \gamma < 1$) denotes the coefficient of conflict, and F denotes the two-body interaction. For the concrete form of the function F , which denotes the two-body interaction between ECs, we adopt the followings:

$$(2.3) \quad F(x) := \begin{cases} \operatorname{sgn}(x)f_r & (0 < |x| \leq R_r) \\ -\operatorname{sgn}(x)f_a & (R_r < |x| \leq R_a) \\ 0 & (R_a < |x|) \end{cases}$$

where $\operatorname{sgn}(x)$ is the sign function, i.e., $\operatorname{sgn}(x) := \frac{x}{|x|}$ for $x \neq 0$ and $\operatorname{sgn}(0) := 0$. The positive constants f_r and f_a represent interaction strengths.

Now let us consider the process of elongation and bifurcation of vessels. From the observation listed above, we consider the following algorithm for elongation and bifurcation. The blood vessel network we consider is the early stage of angiogenesis constructed by ECs and may be modeled by tree-like graphs. The first neogenetic vessel is referred to the branch with index 1, and the branches appeared by bifurcations are indexed by positive integers in order. The index of the branch in which n th EC exists at $t \in \mathbb{Z}_{\geq 0}$ is denoted by $\mu(n, t) \in \mathbb{Z}_+$, and the position of the EC is denoted by the same notation $x_n^t (\geq 0)$ which, however, is measured from the origin of the branch $\mu(n, t)$. The position of the tip of the branch ν is denoted by $b_\nu^t (> 0)$. Then, we introduce three new parameters X_e , $X_b (> 0)$, and $L_b \in \mathbb{Z}_{>0}$, which indicate the threshold impulse for

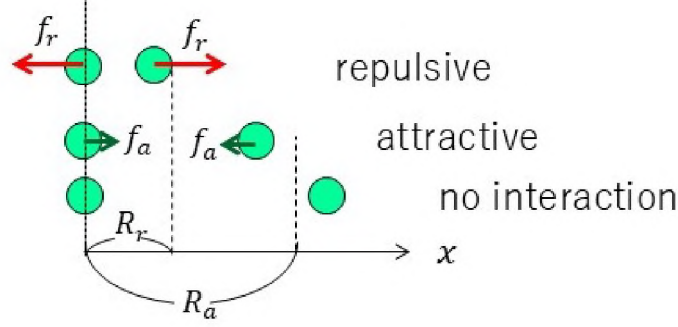


Figure 1. Interaction between two ECs.

elongation, that for bifurcation, and threshold congestion number of ECs at the tip, respectively. When we closely observe the process of bifurcation in experiments, we notice that an EC remains at the tip and other two ECs pass through it, and that one slips through one side of the impassive EC and the other through the opposite side. Hence we impose the condition $L_b = 3$. The time evolution of our discrete dynamical system model is given as follows.

While the first bifurcation has not taken place (*i.e.*, $\forall n, \mu(n, t) = 1$), we put

$$\begin{aligned}\tilde{x}_n^{t+1} &:= x_n^t + v_n^t, \\ \tilde{v}_n^{t+1} &:= v_n^t - \gamma v_n^t + \sum_{k \neq n} F(x_n^t - x_k^t), \\ X^t &:= \sum_{k=1}^{N(t)} \max[0, \tilde{x}_k^{t+1} - b_1^t], \\ L^t &:= \sum_{k=1}^{N(t)} \theta(\tilde{x}_k^{t+1} - b_1^t).\end{aligned}$$

Here $\tilde{x}_n^t$ ($\tilde{v}_n^t$) denotes the provisional position (velocity) of n th EC at time step t , X^t the impulse at the tip, L^t the congestion number at the tip, and θ is the step function:

$$\theta(x) := \begin{cases} 1 & (x > 0) \\ 0 & (x \leq 0) \end{cases}.$$

Note that we set $\tilde{v}_n^{t+1} \rightarrow \pm v_{max}$ when $|\tilde{v}_n^{t+1}| > v_{max}$. Then the updating rule is given as

- (1) if $X^t < X_e$, $x_n^{t+1} = \min[\tilde{x}_n^{t+1}, b_1^t]$, $v_n^{t+1} = \tilde{v}_n^{t+1}$ for all n and $b_1^{t+1} = b_1^t$.
- (2) Else if $X^t < X_b$ or $L^t < L_b$, then $b_1^{t+1} = b_1^t + \Delta b$, and $x_n^{t+1} = \min[\tilde{x}_n^{t+1}, b_1^{t+1}]$, $v_n^{t+1} = \tilde{v}_n^{t+1}$ for all n . Here Δb is the positive parameter which denotes elongation velocity at a tip of a vessel.

(3) Else, that is, $X_b \leq X^t$ and $L_b \leq L^t$, then the vessel bifurcates into two branches. We put $b_1^{t+1} = b_1^t$, $b_2^{t+1} = b_1^t + \Delta b$, and $b_3^{t+1} = b_1^t + \Delta b$. Hence $b_1^{t+s} = b_1^t$ for $s \geq 1$. Let $\mathcal{K} := \{k_1, k_2, \dots, k_m\}$ be the set of indices of ECs which satisfy $\tilde{x}_{k_i}^{t+1} > b_1^t$. Without loss of generality, we can assume that $\tilde{x}_{k_1}^{t+1} \leq \tilde{x}_{k_2}^{t+1} \leq \dots \leq \tilde{x}_{k_m}^{t+1}$. Then, the following rule is applied.

(3-a) If $n \notin \mathcal{K}$, $x_n^{t+1} = \tilde{x}_n^{t+1}$, $v_n^{t+1} = \tilde{v}_n^{t+1}$ and $\mu(n, t+1) = 1$.

(3-b) If $n \in \mathcal{K}$, then $x_{k_1}^{t+1} = b_1^t$, $v_{k_1}^{t+1} = 0$, $\mu(k_1, t+1) = 1$, $x_{k_{2i}}^{t+1} = b_1^t + \Delta b$, $v_{k_{2i}}^{t+1} = \tilde{v}_{k_{2i}}^{t+1}/2$, $\mu(k_{2i}, t+1) = 2$, $x_{k_{2i+1}}^{t+1} = b_1^t + \Delta b$, $v_{k_{2i+1}}^{t+1} = \tilde{v}_{k_{2i+1}}^{t+1}/2$, and $\mu(k_{2i+1}, t+1) = 3$ ($i = 1, 2, \dots$).

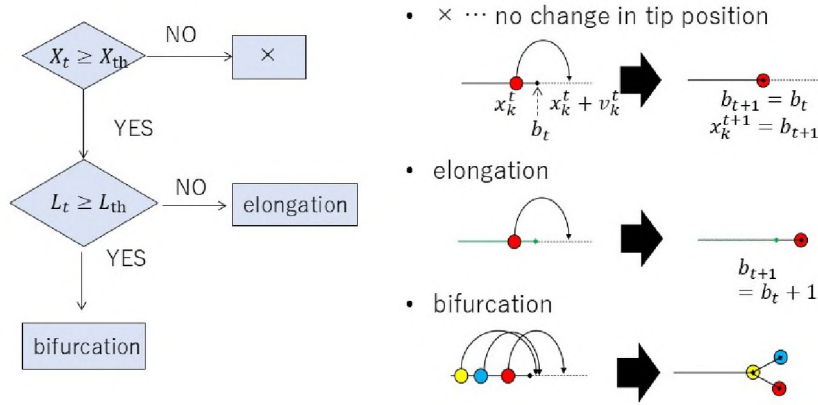


Figure 2. Updating algorithm for elongation and bifurcation.

After the bifurcation has occurred, the above update rules are applied to the ECs on each branch. Two ECs on separate branches can only interact if one branch has bifurcated from the other. At the bifurcation point, the ECs are assumed to move to the branch with the stronger attraction from the other branch. If the strength of the attraction is equal, the ECs will choose one of them with equal probability. Clearly the condition $X_e < X_b$ must be fulfilled and the order of magnitude of X_e and X_b is considered to be the same as the order of the repulsive force f_r . The parameter X_e also depends on the stiffness of the collagen gel in which the ECs are cultured, or on the stiffness of the extracellular matrices in vivo experiments. The injection rate a depends on the size of the source (existing vessels). It is also influenced by enzymes that control cell proliferation, such as VEGF, and the parameters X_e, X_b by the activation of pseudopodia by these enzymes. The parameter Δb gives the scale of an overall vessel network and does not change the pattern of its shape. Hence we set $\Delta b = 1$ in numerical simulations. The typical growth patterns of blood vessels in the present model are shown in Figure 3, where small colored discs denote the positions of nuclei of ECs,

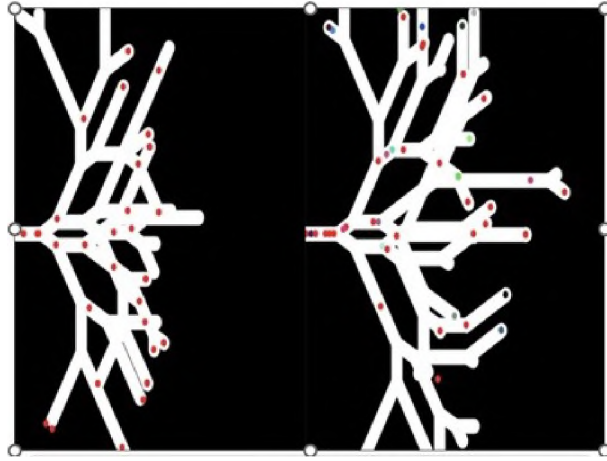


Figure 3. A network pattern obtained from the 1D model. Reconnection of vessels is taken into account. Proliferation of ECs is also considered in the right figure.

white tubes denote the neogenetic vessels. These figures can be seen as a projection of the vascular network onto a two-dimensional plane. In addition, the original model did not incorporate the effect of reconnection, whereas these figures are based on a model that also incorporates the effect of vessel reconnection.

The continuous approximation of the above discrete one dimensional model has been investigated[14]. The model consists of simultaneous differential equations. It includes several exactly solvable cases. Multi-fractal analysis is performed and the network patterns obtained by incorporating reconnection are found to have fractal features.

§ 3. Two dimensional elliptic particle model and its three dimensional extension

The previous model for angiogenesis is essentially one-dimensional, and bifurcation is given algorithmically. A model is preferable in which bifurcation is induced solely by interactions between ECs. ECs move by extending pseudopodia. So it is reasonable to assume that the interaction of pseudopodia between cells generates a self-propagating force in those cells. To incorporate the anisotropy of cell shape caused by the extension of pseudopodia, each cell is assumed to be described as an ellipse on a plane. Now that we are considering the interaction of two ellipses, we need to determine the collision of the ellipses. First, we discuss a numerical procedure to determine the collision of ellipses, and then we discuss a mathematical model of the dynamics of elliptical particles.

Let a_i and b_i be the major and minor axes of the i -th cell (hereafter called “cell- i ”), respectively. The two-dimensional coordinates of the boundary (ellipse) of the cell- i are

expressed as

$$(3.1) \quad \begin{pmatrix} x_i(\theta) \\ y_i(\theta) \end{pmatrix} = \mathbf{r}_i + \begin{pmatrix} \cos \psi_i & \sin \psi_i \\ \sin \psi_i & \cos \psi_i \end{pmatrix} \begin{pmatrix} a_i & 0 \\ 0 & b_i \end{pmatrix} \begin{pmatrix} \cos \theta \\ \sin \theta \end{pmatrix} \quad (0 \leq \theta < 2\pi),$$

where $\mathbf{r}_i \in \mathbb{R}^2$ and $\psi_i \in [0, \pi)$ denote the position of center of gravity and inclination of the major axis of cell- i , respectively. For $D \in \mathbb{Z}_{>0}$ and $\theta_k := 2\pi k/D$, we take D sampling points on the ellipse of cell- i as ${}^t(x_i(\theta_k), y_i(\theta_k))$ ($k = 0, 1, \dots, D-1$). Cells i and j are considered to be in contact when some sampling point on the ellipse of cell- i is inside the ellipse of cell- j . Since the ellipse is given by a quadratic equation, it is easy to check whether the sampling point is inside the ellipse.

The state of cell- i at time step $t \in \mathbb{Z}$ ($t \geq 0$) is characterized by its position $\mathbf{r}_i^t \in \mathbb{R}^2$, velocity $\mathbf{v}_i^t \in \mathbb{R}^2$ and inclination of longer axis $\psi_i^t \in [0, \pi)$. We consider the following discrete dynamical systems.

$$(3.2) \quad \mathbf{r}_i^{t+1} = \mathbf{r}_i^t + \mathbf{v}_i^t,$$

$$(3.3) \quad \mathbf{v}_i^{t+1} = \mathbf{v}_i^t - \gamma \mathbf{v}_i^t + \sum_{j \neq i} \mathbf{F}_{i,j}^t,$$

$$(3.4) \quad \psi_i^{t+1} = \psi_i^t - \sum_k' f_p \sin 2\theta_k,$$

where the parameter $\gamma > 0$ denotes the coefficient of conflict, $\mathbf{F}_{i,j}^t$ denotes the two-body interaction, f_p is a positive constant, and $\sum_k'$ denotes the summation over all sampling points θ_k of cell- i contained inside the ellipse of cell- j .

For the force $\mathbf{F}_{i,j}^t$, similarly to the one-dimensional model, we adopted the following form (Fig. 4):

- (i) If sampling points on the ellipse of the cell- i are in that of the cell- j , then $\mathbf{F}_{i,j}^t = f_r \mathbf{e}_{i,j}^t$
- (ii) Else, if $\|\mathbf{r}_i^t - \mathbf{r}_j^t\| \leq R_a$, then $\mathbf{F}_{i,j}^t = -f_a \mathbf{e}_{i,j}^t$
- (iii) Otherwise $\mathbf{F}_{i,j}^t = \mathbf{0}$.

Here, R_a is the threshold for the attraction, $\mathbf{e}_{i,j}^t := (\mathbf{r}_i^t - \mathbf{r}_j^t) / \|\mathbf{r}_i^t - \mathbf{r}_j^t\|$ and f_a, f_r are the positive constants for the strength of interaction. We assumed $f_r > f_a > 0$ due to the excluded volume effect.

Equation (3.2) and (3.3) show the discrete analogue of the Newtonian equation of motion as in the one-dimensional model. Equation (3.4) means that when two elliptic particles come into contact, their major axes rotate in a direction that avoids collision. The parameter f_p in equation (3.4) controls the orientation of the ellipse. When $f_p = 0$, the particles do not rotate at all, and as the value of f_p increases, they rotate more easily.

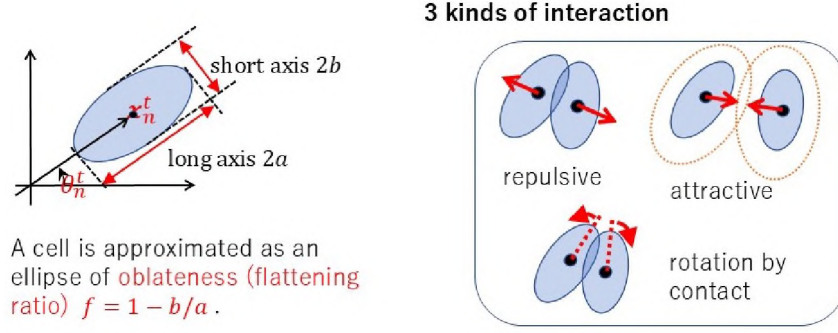


Figure 4. Elliptic particle and interactions between them.

We show examples of the time evolution of 500 elliptic particles with oblateness $f = 0.2$ and 0.8 . Round particles ($f = 0.2$) always aggregate in the case of random distribution (Fig. 5 and that of constant supply (Fig. 6). In contrast, elongated particles form network structures observed in vasculogenesis (Fig. 5), and branch-like structures observed in angiogenesis (Fig. 6). In both cases, we obtain network or branch-like structures for elongated elliptic particles with $f = 0.8$.

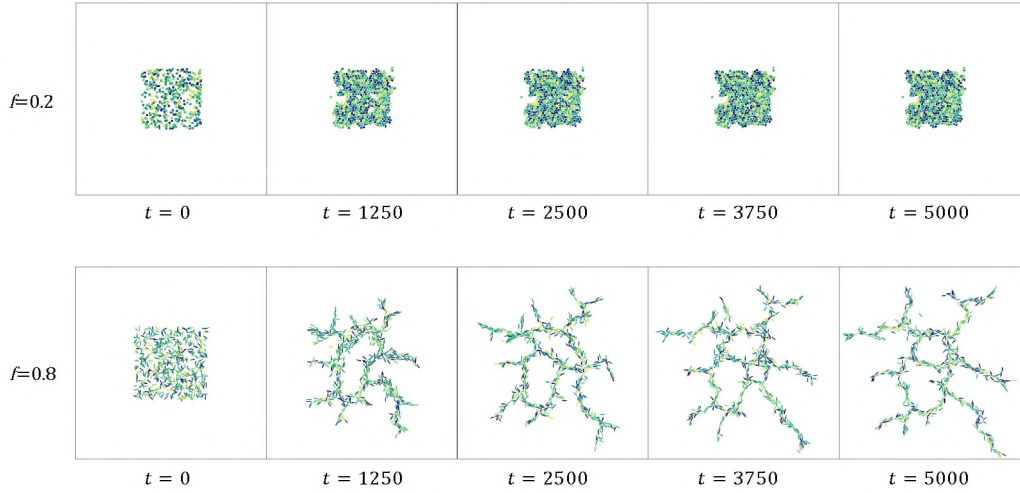


Figure 5. Temporal pattern change of elliptic particle models starting from random distribution of 500 ECs. Upper figures show the case for oblateness $f = 0.2$, and lower figures $f = 0.8$.

These results suggest that the shape of a particle is essential to construct network structures. In addition, we have shown that the rotation of a particle also significantly affects pattern formation and the elongation of sprouts. These results suggest that alignment of ECs by moderate rotation is essential to elongation of branch structures.

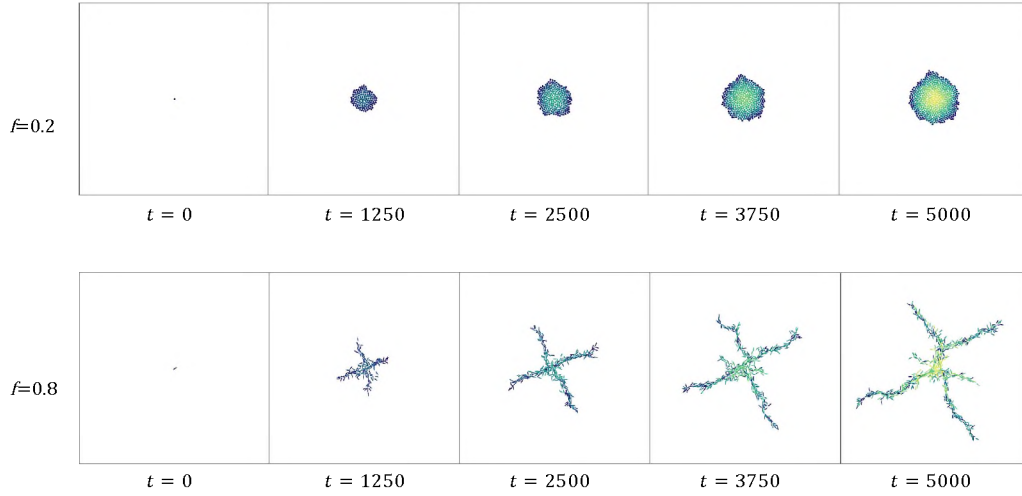


Figure 6. Temporal pattern change of elliptic particle models by injecting particle at a constant rate up to 500 ECs. Upper figures show the case for oblateness $f = 0.2$, and lower figures $f = 0.8$.

The above two dimensional elliptic particle model can be extended to three dimensional ellipsoid particle models. The interactions are essentially the same though we have to consider in three spatial dimensions. Here we only show numerical results.

Figures 7 show network patterns depending on the oblateness f obtained by the three dimensional ellipsoid model. Here we assume that the two short axes are the same length. In this numerical simulation, we start no cells at $t = 0$, and a single cell is introduced at the origin every 10 time steps up to 25000 time steps. The initial velocity of an introduced cell is zero, and its major axis direction is randomly selected. The final patterns strongly depend on the oblateness of the ellipsoid. In actual ECs, the oblateness is measured as $0.6 \sim 0.8$, which coincides with the present results. Thus we see that the shape of ECs is an important factor for network constructions.

§ 4. Concluding remarks

In this article, we have reviewed discrete dynamical mathematical models for angiogenesis. Based on the observation in in vitro experiments, these models reproduce cell-mixing phenomena and elongation and bifurcation. In the present models for two and three spatial dimensions, an EC is represented by an elliptic or an ellipsoidal particle, and the dynamics of ECs is given by a deterministic two-body interactions consisting of attraction and repulsion, and a rotation at contact. The attraction represents the driving force originating from contact between ECs via the pseudopodia, while the repulsion is due to the exclusion volume effect. Rotation during contact is thought to be due

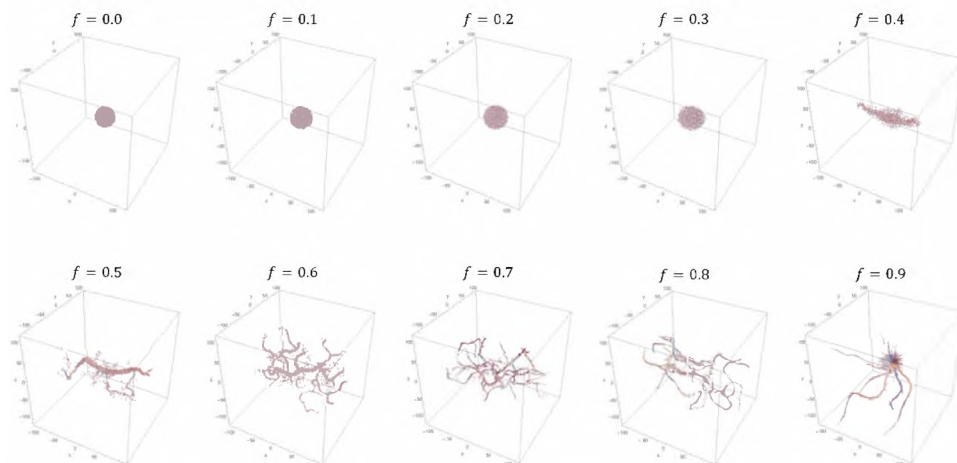


Figure 7. Oblateness (f) dependence of final net work patterns of three dimensional ellipsoid model. Particles (ECs) are injected at the center every 10 time steps up to 25000 steps.

to both the exclusion volume effect and the reaction of the pseudopodia. The oblateness of the particles has a strong influence on pattern formation. Rotation of particles is also shown to have a strong effect on pattern formation and sprout elongation. These results suggest that the alignment of ECs by moderate rotation is essential for elongation of the branch structure. Interestingly, a relatively small number of elliptic particles align in a straight line. In the early stages of angiogenesis, a small number of vascular endothelial cells form sprouts in the extracellular matrix. We would like to improve these models by incorporating more realistic biological conditions, such as extracellular matrices and VEGF, to quantitatively clarify EC dynamics during angiogenesis and to use it for in silico experiments in the medical field.

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