Mathematical Modelings for Angiogenesis – A Cellular Automaton Model and its Continuous Model

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Abstract

Based on recent experiments with time-lapse fluorescent imaging, we propose a cellular automaton model for the dynamics of vascular endothelial cells (ECs) in angiogenic morphogenesis. The model successfully reproduces cell mixing behavior, elongation and bifurcation of blood vessels. The results suggest that the two-body interaction between ECs, which is repulsive in short distance and become attractive in moderately long distance, is essential to the dynamics of ECs, in particular, to the cell mixing behavior. The corresponding analytically solvable differential equation model is also proposed.

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The extensive network of blood vessels throughout the body is established by angiogenesis, a multicellular process of branch elongation and bifurcation driven by the collective movement of vascular endothelial cells (ECs). Angiogenic elongation was commonly regarded as a quasi-static phenomenon in which an EC is selected to be ‘a tip cell’ with filopodia, and goes ahead at the top of ECs\cite{1, 2}. The adjacent ECs are assumed to follow the tip cell as stalk cells connected to each other with cell-cell junctions. Recent experiments with time-lapse live imaging, however, have revealed unexpected movement of ECs in elongation and bifurcation of vessels\cite{3, 4}. Individual ECs are observed to move back and forth along the path of the elongation in stalks and junctions and often change their positions even at the tips. This cell-mixing effect was observed both in vitro and vivo experiments. This result suggests that the interaction between ECs during angiogenesis is more dynamic and complicated than ever thought. This result implies that the interaction between ECs is essential in multicellular dynamics in angiogenesis.

A lot of models for angiogenesis have been proposed from various points of view \cite{5–8}. In the previous models, particularly in single-cell based models\cite{9}, emphasis is mostly put on the pattern formation of vessel networks where chemoattractant gradient and chemotaxis of ECs play essential roles \cite{10–12}. In this article, motivated by the experimental results stated above, we wish to investigate mathematical modeling for the dynamics of ECs in the early stage of angiogenesis. Our purpose is to construct a simple mathematical model which reproduces the cell-mixing behavior, elongation, and bifurcation of vessels without chemotaxis because no gradient of angiogenic factors such as vascular endothelial growth factor (VEGF) is required for branching morphogenesis in the experimental settings. Although angiogenesis is a multicellular phenomenon involving a lot of factors, such a complex dynamics can be well simulated by a cellular automaton (CA) model, which exhibits various complex spatiotemporal patterns by simple updating rules\cite{13}. In the CA model of traffic flow, well-known and successful example of CA modeling\cite{14, 15}, a vehicle on a lane is modeled by a state of one of one dimensional array of cells, which is updated in discrete time steps, or, equivalently, by a non-individual particle sitting on the array of cells, which moves to another cell in discrete time steps by an updating rule. CAs are also used in many fields of biology\cite{16}, for example, as a model for tip growth of a fungus\cite{17}. Here we also propose a CA model based on the experimental findings of EC dynamics and show that it can exhibit the expected behavior of ECs. Our CA model is similar to that of traffic flow at
the point that an EC is modeled as a non-individual particle but it is quite different since no elongation nor bifurcation of a traffic lane takes place in traffic flow. Although there may be stochastic fluctuation in the EC dynamics, we suppose that its effect is not essential and our CA model is deterministic. In the latter part of this paper, we deduce from the CA model a differential equation model which depends only on the density of ECs. We show that this continuous model can be solved analytically and is applicable to other biological systems because of its simplicity and versatility.

CELLULAR AUTOMATON MODEL

Let us define the variables and notations we use in our CA model. We suppose that ECs are supplied from the source (the existing blood vessel) at a constant rate \( a \in \mathbb{Z}_{>0} \). We do not take cell division into account, for it is rarely observed in the time span of the experiments (5% per day). Hence, the \( n \)th \((n = 0, 1, 2, \ldots)\) EC is supplied to the origin of the newly generated vessel networks at time step \( t = na \) with an initial velocity \( v_{ini} \in \mathbb{Z}/M \). Here the parameter \( M \) is a positive integer which is put \( M = 20 \) in our simulation. At \( t = 0 \), one neogenetic vessel with length greater than \( v_{ini} \) exists and elongates and bifurcates with the supply of ECs. The first neogenetic vessel is referred to the branch with index 1, and the branches emerged 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 \( \mu(n, t) \in \mathbb{Z}_{>0} \), and the position of the EC is denoted by \( x_t^n \in \mathbb{Z}_{\geq 0}/M \) which is measured from the origin of the branch \( \mu(n, t) \). The position of the tip of the branch \( \nu \) is denoted by \( b^\nu_t \in \mathbb{Z}_{>0}/M \).

Important observations in the experiments are (a) ECs show the cell mixing effect, (b) bifurcation occurs mostly at the tip when the tip is crowded by ECs, and (c) a vessel splits into two branches with an angle of approximately 60 degrees \[^3\]. For short distance, the interaction force is repulsive due to the excluded volume effect, while it becomes attractive if the distance becomes larger because of the interaction with pseudopodia. Accordingly, we consider the following equations of motion of ECs in a branch

\[
x_t^{n+1} = x_t^n + v_t^n
\]

\[
v_t^{n+1} = v_t^n - \gamma v_t^n + \sum_{k \neq n} F(x_t^n - x_t^k)
\]

where the parameter \( \gamma \in \mathbb{Z}/M \) \((0 < \gamma < 1)\) denotes the coefficient of conflict and \( F \) denotes
the two-body interaction which is defined as

\[
F(x) := \begin{cases} 
\text{sgn}(x)f_r & (0 < |x| \leq R_r) \\
-\text{sgn}(x)f_e & (R_r < |x| \leq R_e) \\
-\text{sgn}(x)f_a & (R_e < |x| \leq R_a) \\
0 & (R_a < |x|) 
\end{cases}
\] 

(3)

where \(\text{sgn}(x) := \frac{x}{|x|}\), \(R_r, R_e, R_a\) are the positive integers which denote interaction ranges, \(f_r, f_e, f_a \in \mathbb{Z}_{>0}/M\) are the positive rational constants and we assume \(f_r > f_e > f_a\). When \(x_n^t = x_k^t\), we set

\[
F(x_n^t - x_k^t) = \text{sgn}(x_n^t - x_k^t)f_r,
\]

that is, we suppose that the interaction depends on the previous positions of the ECs in this case. Equation (1) means that \(v_n^t\) is the velocity of the \(n\)th EC at time step \(t\), while Eq. (2) is the CA analogue of the Newtonian equation of motion:

\[
\frac{d^2x_n(t)}{dt^2} = -\gamma \frac{dx_n(t)}{dt} + \sum_{k \neq n} F(x_n(t) - x_k(t))
\]

Dynamics of ECs near tips and junctions are also given by straightforward generalization of Eqs. (1) and (2) with the elongation and bifurcation rules below. We suppose that two ECs can interact only when they are in the same branch or one of them is in a tributary branch to that of the other ECs.

In view of the observation (b), we introduce three new parameters \(X_e, X_b \in \mathbb{Z}/M\), and \(L_b(\geq 3) \in \mathbb{Z}_{>0}\), which indicate the threshold impulse for elongation, that for bifurcation, and threshold congestion number of ECs at the tip, respectively. The updating rule of our CA model is determined as follows (Fig. 1).

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

\[
\begin{align*}
\tilde{x}_{n+1}^t &:= x_n^t + v_n^t \\
\tilde{v}_{n+1}^t &:= v_n^t - \gamma v_n^t + \sum_{k \neq n} F(x_n^t - x_k^t) \\
X^t &:= \sum_{k=1}^{N(t)} \max[0, \tilde{x}_k^t - b_1^t] \\
L^t &:= \sum_{k=1}^{N(t)} \theta(\tilde{x}_k^t - b_1^t)
\end{align*}
\]
Here $\tilde{x}_n^t (\tilde{v}_n^t)$ denotes the provisional position (velocity) of $n$th EC at time step $t + 1$, $X^t$ the impulse at the tip, $L^t$ the congestion number at the tip, and $\theta$ is the step function:

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

Then, if $X^t < X_e$, $x_n^{t+1} = \tilde{x}_n^t$, $v_n^{t+1} = \tilde{v}_n^t$ for all $n$ and $b_1^{t+1} = b_1^t$.

(ii) Else if $X_e \leq X^t$ and $X^t < X_b$ or $L^t < L_b$, then $b_1^{t+1} = b_1^t + 1$, and $x_n^{t+1} = \min[\tilde{x}_n^t, b_1^{t+1}]$, $v_n^{t+1} = \tilde{v}_n^t$ for all $n$.

(iii) Else, that is, $X_e \leq X^t$, $X_b \leq X^t$, and $L_b \leq L^t$, then the vessel bifurcates into two branches. We put $b_1^{t+1} = b_1^t$, $b_2^{t+1} = b_1^t + 1$, and $b_3^{t+1} = b_1^t + 1$. Hence $b_1^{t+1} = b_1^t$ for $s \geq 1$. Let $K := \{k_1, k_2, \ldots, k_m\}$ be the set of indices of ECs which satisfy $\tilde{x}_{k_1}^{t+1} > b_1^t$. We assume $\tilde{x}_{k_1}^{t+1} \leq \tilde{x}_{k_2}^{t+1} \leq \ldots \leq \tilde{x}_{k_m}^{t+1}$. Then, if $n \notin K$, $x_{k_1}^{t+1} = \tilde{x}_{k_1}^{t+1}$, $v_{k_1}^{t+1} = \tilde{v}_{k_1}^{t+1}$ and $\mu(n, t + 1) = 1$. For $n \in K$, $x_{k_1}^{t+1} = b_1^t$, $v_{k_1}^{t+1} = 0$, $\mu(k_1, t + 1) = 1$, $x_{k_2}^{t+1} = b_1^t + 1$, $v_{k_2}^{t+1} = \tilde{v}_{k_2}^{t+1}/2$, $\mu(k_2, t + 1) = 2$, $x_{k_3}^{t+1} = b_1^t + 1$, $v_{k_3}^{t+1} = \tilde{v}_{k_3}^{t+1}/2$, and $\mu(k_3, t + 1) = 3$ ($i = 1, 2, \ldots$). Here if $v_{k}^{t+1} \notin \mathbb{Z}/M$, we subtract $1/2M$ from it.

(iv) After bifurcations took place, we apply the above updating rule to the ECs in each branch. Two ECs in separate branches can interact with each other only if one branch has bifurcated from the other branch. At a junction of bifurcation, we assume that an EC move into one branch from which attractive force is stranger than that from the other branch.

FIGs. 2 show the movement of ECs in a growing branch for three types of interactions. We also show the distribution of ECs in the vessel after long time has passed. When interaction is only repulsive, the distribution of ECs is fairly uniform but cell-mixing behaviour is not seen very often as shown in FIG. 2 (I), while if interaction is only attractive, ECs clump together as in FIG. 3 (II). On the other hand, when both repulsive and attractive interactions coexist
FIG. 2. Trajectories of EC movements during elongation with parameters $R_r = 0.1, R_e = 0.4, R_a = 0.7, \gamma = 0.6, a = 5, v_{ini} = 0.3$ and (I) $f_r = 0.45, f_e = -0.25, f_a = -0.05$, (II) $f_r = -0.45, f_e = 0.25, f_a = 0.05$ and (III) $f_r = 0.45, f_e = 0.25, f_a = 0.05$.

FIG. 3. Distributions of ECs at time step $t = 5000$. Parameters are the same as those in FIG. 2 as is supposed in our model, ECs clearly show cell-mixing behavior and the distribution of ECS is sufficiently uniform. Hence we conclude that both repulsive and attractive interaction between ECs are essential in the dynamics of ECs. The growth of blood vessels in the present model is shown in FIG. 4 and FIG. 5 where we take the observation (c) into account.

In FIG. 6 we show dependence of the length of first blood vessel, i.e., the length between the origin of the blood vessel and the first junction, on the parameters $X_e$ and $X_b$. The larger the threshold for bifurcation $X_b$ becomes, the longer the length of blood vessel tends to be. For the elongation threshold $X_e$, the inverse dependence is observed.

The behavior of ECs and evolution patterns of new vessels in early stage are well reproduced by the present CA model. However, since we do not incorporate recombination of vessels and cell division, the time evolution patterns for long time span deviate from actual networks of blood vessels. In particular, the length of vessels tends to be longer with increase of bifurcations, which is not observed in actual systems. We conjecture that this discrepancy
FIG. 4. A simulation of angiogenesis using our CA model with $X_e = 1.3, X_b = 1.8, L_b = 3, f_r = 0.45, f_e = 0.25, f_a = 0.05, R_r = 0.1, R_e = 0.4, R_a = 0.7, \gamma = 0.6, a = 5, v_{ini} = 0.3$. White dots denote positions of nuclei of ECs.

FIG. 5. A simulation with different parameters, where $X_e = 3.0, X_b = 3.2, L_b = 3, f_r = 0.45, f_e = 0.25, f_a = 0.05, R_r = 0.1, R_e = 0.4, R_a = 0.7, \gamma = 0.6, a = 5, v_{ini} = 0.3$.

FIG. 6. The length of the first blood vessel is shown for various parameters $X_e$ and $X_b$. The other parameters are fixed as $L_b = 3, f_r = 0.45, f_e = 0.25, f_a = 0.05, R_r = 0.1, R_e = 0.4, R_a = 0.7, \gamma = 0.6, a = 5, v_{ini} = 0.3$.

is caused by the effect of cell division which was rarely observed in the time-lapse imaging experiments, but will be important for long time span.
DEFERENTIAL EQUATION MODEL

The present CA model successfully reproduced effects of cell-mixing, elongation and bifurcation. It is, however, not suitable for estimation of branching time, length of blood vessels, density of ECs and so on due mainly to the discrete nature of the CA model. To discuss quantitative estimation of those physical properties as well as parameter dependence and global behavior of the system, we wish to construct an analytically tractable continuous model based on the results of the previous section. One of the most important factors in the CA model presented above is the density or the number of the ECs at the tip, by which the morphogenetic behavior of blood vessels is determined. Hence, we propose the following continuous model defined by differential equations which may be regarded as quasi-static approximation to the coarse-graining of the CA model. The assumptions made for the continuous model are; (i) elongation and bifurcation are determined only by the number of ECs at the tip, (ii) the density of ECs is spatially uniform and depends on time, and (iii) ECs are supplied at a constant rate from the stem blood vessel. Let \( N(t) \) be total number of ECs at time \( t \) supplied into new vessels. Then, from the assumption (iii), we have

\[
N(t) = N_{ini} + a(t - t_0)
\]

where \( a \) is the positive constant and \( N_{ini} \) is the initial number of ECs at \( t = t_0 \). Without loss of generality, we can put \( t_0 = N_{ini}/a \) and we have

\[
N(t) = at
\]  

(4)

Note that (4) means that we do not take the effect of cell division now.

We denote by \( L_k^{(i)}(t) \) the length of the \( i \)th blood vessel \((1 \leq i \leq 2^k)\) which appears after \( k \) times bifurcations. We hereafter call it the \((k, i)\) vessel and denote by \( s_k^{(i)} \) the cross section of the \((k, i)\) vessel. Then, the density of ECs \( \rho(t) \) is given by

\[
\rho(t) = \frac{N(t)}{\sum_k \sum_i s_k^{(i)} L_k^{(i)}(t)},
\]

(5)

and the number of ECs at the tip of \((k, i)\) vessel is

\[
n_k^{(i)}(t) = \rho(t)s_k^{(i)}l
\]

(6)

where \( l \) denotes the effective length of the tip. Here we suppose that cross sections of blood vessels decrease after bifurcation, that is, \( s_k^{(i)} > s_{k+1}^{(j)} \) if the \((k + 1, j)\) vessel emerges from the \((k, i)\) vessel.
According to the updating rule for the CA model, the velocity of elongation is assumed as

\[
\frac{d}{dt} L_k^{(i)}(t) = \begin{cases} 
  v_0 \left( n_k^{(i)}(t) - n_e \right) & \text{if } (n_k^{(i)}(t) \geq n_e) \\
  0 & \text{if } (n_k^{(i)}(t) < n_e)
\end{cases}
\]

(7)

where \( v_0 \) and \( n_e \) are positive constants, and if \( n_k^{(i)}(t) \geq n_b \), then the vessel bifurcates into two branches. Here \( n_b \) \(( \geq n_e \) is the threshold value of bifurcation. In general, elongation rate \( v_0 \), the threshold \( n_e \) and \( n_b \) may depend on the branches. Even in these general cases, the following analysis hold in a similar manner without difficulty. From (5), (6) and (7), we have

\[
\frac{d}{dt} p(t) = V_m (\rho(t) - \rho_e)
\]

(8)

where \( V_m := \frac{v_0 \sum \alpha(s_k^{(i)})^2}{\sum \alpha} \), \( \rho_e := \frac{n_b}{\sum \alpha(s_k^{(i)})^2} \) and \( \sum \alpha \) denotes the summation over the indices \((k,i)\) which satisfy \( n_k^{(i)} \geq n_e \). Equation (8) is a simple differential equation for \( \rho(t) \), and we can analytically integrate it. Then we obtain analytical expressions for the times of bifurcations, lengths of branches, and so on. Note that the constants \( V_m \) and \( \rho_e \) change in time discontinuously when the number of ECs at a tip exceeds the threshold values. Defining positive constants \( \alpha, \beta \) by

\[
\beta - \alpha = \rho_e, \quad \alpha \beta = \frac{1}{V_m}
\]

the integration from \( t = t_i \) to \( t_f \) gives

\[
\frac{t_f}{t_i} = \left( \frac{\rho(t_f)}{\rho(t_i)} \right) \left( \frac{\rho(t_f) + \alpha}{\rho(t_i) + \alpha} \right)^{\frac{\alpha}{\beta}} \left( \frac{\beta}{\alpha} \right)^{\frac{\alpha}{\beta}}
\]

(9)

While the vessels are elongating, new bifurcation takes place at the tip of \((k^*, i^*)\) vessel at time \( t^* \) under the conditions \( s_k^{(i^*)} := \max_k \left( \max_i \left[ s_k^{(i)} \right] \right) \) and \( \rho(t^*) s_k^{(i^*)} l = n_b \). The length of the branches can be determined by (5), (6) and

\[
\frac{d}{dt} \left[ s_k^{(j)} L_k^{(i)}(t) - s_k^{(j)} L_j^{(p)}(t) \right] = v_0 n_e (s_j^{(p)} - s_k^{(i)})
\]

for arbitrary two growing branches \((k,i)\) and \((p,j)\). FIG. 7 shows an example of the growth pattern of blood vessels obtained from this continuous model.

In particular, if all the cross sections of the branches emerged at the \( k \) times bifurcations are equal, that is, \( s_k^{(i)} = s_k \) for all \( i \), then the \( k \) times bifurcation takes place at the same time \( t_k \) which is determined by \( s_{k-1} l \rho(t_k) = n_b \). Defining \( \alpha_k \) and \( \beta_k \) by \( \beta_k - \alpha_k = \frac{n_e}{l s_k} \), \( \alpha_k \beta_k = \frac{1}{V_m} \)
FIG. 7. An example of the growth pattern of blood vessels with $a = 3, l = 5, v_0 = 0.1, n_e = 1, n_b = 3, L_{ini} = 0.7, t_0 = 0.1$ and $0.5 \lesssim s_k^{(i)} \leq 3$.

Here $s_{-1} := \frac{n_b}{\rho(t_0)}$ and we assumed that $n_k(t_k) = \rho(t_k)s_k l \geq n_e$ for simplicity. In case of $n_k(t_k) < n_e$, we have only to replace $t_k$ with $t^* := \frac{n_k V_k}{a s_k l}$, where $V_k$ is the total volume of the vessels at $t_k$. If we denote by $L_k$ the length of the branch which emerges at $k$ times bifurcation, that is, the branches which grow during $t_k < t \leq t_{k+1}$, we have $L_0 = \frac{a t_{ini}}{n_b}$, and $L_k = \frac{a(t_{k+1} - t_k)}{2n_b}$.

So far we have not considered the effect of cell division, and, as observed in the CA model, the length of branches become longer with bifurcations. In fact, the asymptotic behavior of (8) shows that the number of bifurcations is finite. In the case of uniform cross sections discussed above, no bifurcation takes place for $s_k \beta_k < n_b$. Thus, the number of bifurcations does not depend on the cross sections as far as the condition $s_{i+1} < s_i (i = 0, 1, 2, ...)$ is satisfied. Accordingly, $n_k^{(i)}(t) = n_k(t)$ for all $i$ and the $k$ bifurcation takes place at the same time $t_k$ which is determined by $n_{k-1}(t_k) = n_b$. The equation for $n_k(t) (t_k \leq t \leq t_{k+1})$ is given

$$\frac{d n_k(t)}{dt} = -\frac{v_0 a^2}{atl} n_k(t)(n_k(t) - \mu_k)(n_k(t) + \nu_k)$$

where

$$n_k(t_k) = \begin{cases} \frac{a t_{ini} s_k}{V_k} & (k \geq 1) \\ \frac{N_{ini} s_0}{L_{ini}} & (k = 0) \end{cases},$$

$$\mu_k = \frac{n_e}{2} + \sqrt{\frac{n_e^2}{4} + \frac{a l}{v_0^2 2k}}, \quad \nu_k = -n_e + \mu_k, \quad V_k = \sum_{j=0}^{k-1} 2^j s_j L_j$$

and $L_j$ is the length of $j$th branch of blood vessel. Here we assumed $n_k(t_k) \geq n_e$ for simplicity. In case of $n_k(t_k) < n_e$, we have only to replace $t_k$ with $t^*_k := \frac{n_k V_k}{a s_k l}$. From (11),
we can analytically obtain $L_k, t_k$ and so on. In particular, from the asymptotic behavior of (11), we find that the number of bifurcation does not depend on the cross sections and is given

$$\left\lfloor \log_2 \left( \frac{al}{v_0 n_b (n_b - n_e)} \right) \right\rfloor$$

However, if we consider the cell division process, (4) should be replaced with the equation

$$\frac{dN}{dt}(t) = a + \epsilon N(t)$$

where $\epsilon$ is the rate of cell division. Then (8) is rewritten as

$$(a + \epsilon N) \frac{d}{dN} \left( \frac{N}{\rho} \right) = aV_m (\rho - \rho_e)$$

Since $N(t)$ is an exponentially increasing function of $t$, we easily find that the number of bifurcation is not limited. This fact suggests that the effect of cell division becomes significant in long time span. It might be more realistic if we consider a Logistic type equation instead of (12). In this case, elongation and bifurcation will gradually stop when $N(t)$ reaches a saturation value.

**CONCLUSION**

In conclusion, we have presented a deterministic CA model for angiogenesis which successfully reproduces the cell mixing behavior, elongation and bifurcation. The dynamics of ECs is supposed to be mainly ruled by two body interactions which consist of short-range repulsion due to excluded volume effect and long-range attractive force through pseudopodia. We also constructed a continuous model based on the CA model, which can be treated analytically and physical quantities such as the number of bifurcation are obtained as functions of the parameters in the system. This also suggests that the effect of cell division is important in constructing vessel networks. This continuous model may be applicable to other systems such as elongation and bifurcation of cartilages in a piscine fin, growth of roots of certain plants, construction of river systems, avalanche of earth and rocks and so on. In the models, we have not, however, included chemotaxis, a gradient distribution of VEGF and remodeling of blood vessels which are important in construction of *in vivo* blood vessel networks. Incorporating these factors and closely examining forthcoming experimental results, we wish to develop the present models so that we can quantitatively explain
various types of angiogenic phenomena and provide a theoretical framework for clinical trials targeting angiogenesis.

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