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Review Article

Theoretical Models of Vascular Pattern Formation

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Abstract

Pattern formation of vascular structure has been extensively studied in vascular biology. Classically the pattern formation process falls into three categories-vasculogenesis, angiogenesis and remodeling. Mathematical modeling study of these phenomena has been done byrelatively independent of experimental works by applied mathematicians, and not well understood by experimental biologists. In this review I provide intuitive explanations of proposed theoretical models and recent advance in modelling study of vascular development.

Key words : vascular pattern formation, theoretical model

Introduction

The mechanism of blood vessel development has been one of major topics in developmental biology. Some researches try to understand the developmental process using mathematical models[1]. Recent advance in computational frameworks and imaging techniques have enabled us to combine experimental and theoretical studies to reproduce the phenomena *in silico* and understand the mechanisms.

In this review, I describe the history and current progress of modeling vascular development. Classically, vascular development is classified into three categories. Vasculogenesis is *de novo* synthesis of the vascular network. Angiogenesis is the addition of new vessel from preexisting vessels. Remodeling is the refinement of the vascular network by changing vessel diameter and arterial-venous differentiation. Theoretical models of each phenomenon have been proposed. Minimal models help us understand the mechanism while computational models reproduce and discover novel aspect of the phenomenon. Combination of both models facilitates the understanding the pattern formation *in vivo*.

Vasculogenesis-cell movement toward regions of high cell density

Vasculogenesis is a process in which endothelial cells form capillary network spontaneously during early phase of development. At first, the progenitor cells form clusters called blood islands, and later they fuse to form meshwork structure[2]. One good *in vitro* model of this phenomenon is human umbilical vein endothelial cells (HUVECs) cultured on Matrigel. In this culture condition, HUVECs connect each other to form meshwork structure within 24 hours (Fig. 1a).

There are various theoretical models to reproduce this *in vitro* vasculogenesis. Most classical one is the

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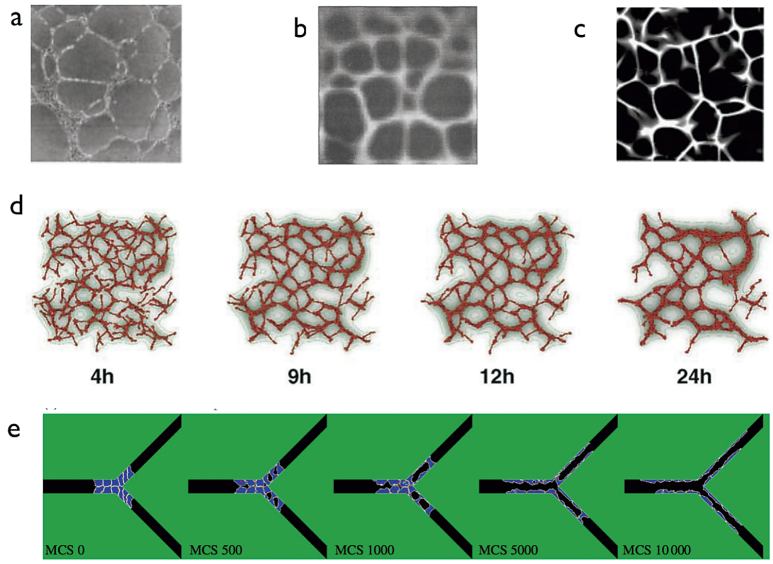

Fig. 1 Models of vasculogenesis. (**a**) Meshwork pattern of HUVECs generated on Matrigel[10]. (**b**) Mechanochemical model of vasculogenesis *in vitro*[3]. (**c**) Continuous model of vasculogenesis[10]. (**d**) Cellular Potts model of vasculogenesis[12]. Red region represents HUVECs and gray shade represents VEGF concentration. The model can reproduce the time course of pattern formation by assuming that each cell has a tendency to be elongated. (**e**) Cellular Potts model of lumen formation[18].

mechanochemical model proposed by James Murray's group in Washington University[3)4)]. In this model, endothelial cells exert traction force and deform Matrigel. As a result, HUVECs move according to the gel deformation. Then, slightly high cell density area, resulting in formation of meshwork structure whose spacing is comparable to the effective length of gel deformation (Fig. 1b).

However, since the discovery of vascular endothelial growth factor (VEGF)[5)], many models incorporate the role of this molecule. VEGF strongly induce endothelial cell chemotaxis and proliferation, and considered to reside on the top of the hierarchy of vascular pattern formation[6)7)]. VEGF expression is induced by hypoxia in general[8)], and endothelial cells themselves also generate VEGF[9)].

A continuous model of pattern formation is proposed[10)11)]. In their model, cells are represented by density distribution, and the distribution changes according to the VEGF gradient and cell proliferation. Intuitive explanation of the pattern formation in this model is as follows : endothelial cells secrete VEGF in a autocrine manner[9)]. VEGF is a major chemoattractant for endothelial cells[5)]. Therefore, endothelial cells tend to be attracted to high cell density area because of chemotaxis, and form clusters whose size is comparable to the length of VEGF gradient (Fig. 1c). One characteristics of their model is that it includes cell velocity field, which means inertia-like effect is considered in the model. They explained that this effect is biologically implemented by cell persistence, a tendency of a cell to move certain direction during short time span. This continuous model is written in the form of partial differential equation (PDE), and easy to be analyzed mathematically.

Another class of models try to express shape of individual cells using cellular Potts framework[12)~15)]. Cellular Potts framework, which is invented by James Glazier in Indiana University, expresses each cell as a cluster of several lattices (pixels). Energy function for volume conservation, cell adhesion and chemotaxis etc. is defined, and lattices are moved stochastically according to the energy function[16)]. Basic mechanism

of pattern formation is the same as that of continuous PDE model–cells produce VEGF and move according to the VEGF gradient. In addition, this model showed that cell elongation is important in generating meshwork structure instead of clusters of endothelial cells[12] (Fig. 1d). Comparing to PDE model, cellular Potts model is difficult to analyze mathematically. However, within this framework we can introduce cell shape dynamics that are directly observed by experiments.

One advantage of incorporating cell shape is that the model can express additional characteristics like lumen formation (Fig. 1e). Formation of lumen is extensively studied in various epithelial cell lines. When epithelial cells are embeded in collagen gel, they spontaneously form lumens[17]. Intuitively, it is because the epithelial cells tend to form polarized structure in which basal surface attached to extracellular matrix and apical surface faces lumen. Endothelial cells have similar tendency, and cellular Potts–based framework is proposed to reproduce lumen formation[18].

Angiogenesis–biased random walk

In later phase of development, sprouting from preexisting blood vessels forms new blood vessels. The process is called angiogenesis[2]. Most classic model of this phenomenon is proposed by Mark Chaplain in University of Dundee[19], and called Chaplain–Anderson model. This model assumes that trajectories of random walk particles with deviation to VEGF source as sprouting vasculatures (Fig. 2a). Equivalent system is well studied in physics[20] and it is easy to understand the dynamics of the system mathematically. Various modifications have been made on this model to explain related phenomena. For example, calculation of flow on the vessel structure generated by Chaplain–Anderson model is done[21,22]. However, it looks too simple for experimental vascular biologists. For example, it is known that cells frequently change their position during pattern formation[23], which is difficult to implement in this framework.

More computational approaches has been carried out recently to include almost all the factors involved in angiogenesis[24]. Their model includes random cell migration, cell adhesion, filopodia, VEGF, VEGFR2, and Dll4 to reproduce the cell dynamics of the growing tip region during angiogenesis. This model reproduces the experimental observation faithfully and is appealing to experimental vascular biologists (Fig. 2b). However, it remains to be elucidated to understand the behavior of the model itself since the model itself is very complex.

Remodeling–flow modifies diameter

Remodeling is the process to generate hierarchic structure from initially uniform network to optimize oxygen and nutrition transport[25]. It has been well known that the blood flow influences the diameter of the vasculatures[26], probably due to shear stress[27]. Importance of shear stress is first mentioned in 1975 by S. Rodbard[28], and the concept was later experimentally verified[29]. The most upstream mechanism for the shear stress sensing is still obscure. Recently P2X4 Ca receptor is reported to play a major role in shear stress sensing[30,31]. Another promising hypothesis is that membrane lipid may directly sense the stress[32].

The first minimal model to reproduce arterial–venous tree structure is formulated by Hisao Honda in Hyogo University[33]. In his model, vessels are represented as edges and nodes of a network structure, and vessel with larger flow became thicker. As a result, differentiation of artery–like structure is reproduced (Fig. 3a). Similar settings were used in another model[34], which can reproduce intermingled pattern of arterial–venous trees (Fig. 3b).

Recently, large–scale computational model that tries to reproduce all the processes of retinal blood vessel development has been proposed[35]. In their model, vasculature is expressed by lattice generated by Chaplain–Anderson model. They calculate pressure and flow distribution in the vessel region. In the retina

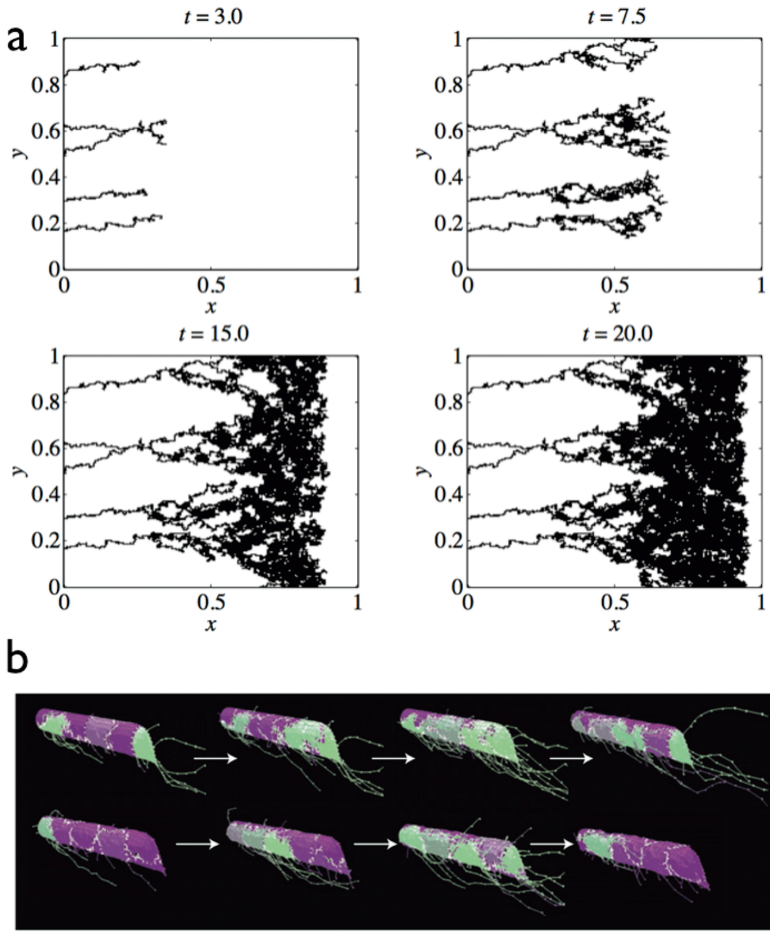

Fig. 2 Models of angiogenesis. (**a**) Chaplain–Anderson model of tumor angiogenesis[19]. Trajectories of random walk particles are regarded as sprouting vasculatures. The probability of the movement is determined by VEGF gradient. (**b**) Agent-based computational model of angiogenesis[48]. The model can reproduce random cell migration, formation of filopodia and Delta-Notch expression (green and purple). Simulation results have one-by-one correspondence with experimental data.

vasculature, artery input and venous output are close to each other, and prevention of shunt is a major problem[36]. They found a parameter set that does not generate shunt in their simulation (Fig. 3c), but mechanism is not yet well understood.

Future directions

Experimental verification of these models can be possible due to technical advances in imaging. Diffusion dynamics of VEGF becomes possible using imaging technique, which is important to estimate the characteristic length of the pattern in chemotaxis-based models[37]. Direct observation of gel deformation in *in vitro* system has been undertaken, and mechanics-based model becomes plausible candidate for the mechanism of pattern formation again[38]. Visualization of cell dynamics in angiogenesis process[23] greatly facilitated our understanding of this process. There are transgenic quail lines with which we can undertake live imaging of cellular dynamics during vascular remodeling process[39]. Direct observation of murine yolk sac vasculature was also undertaken[40].

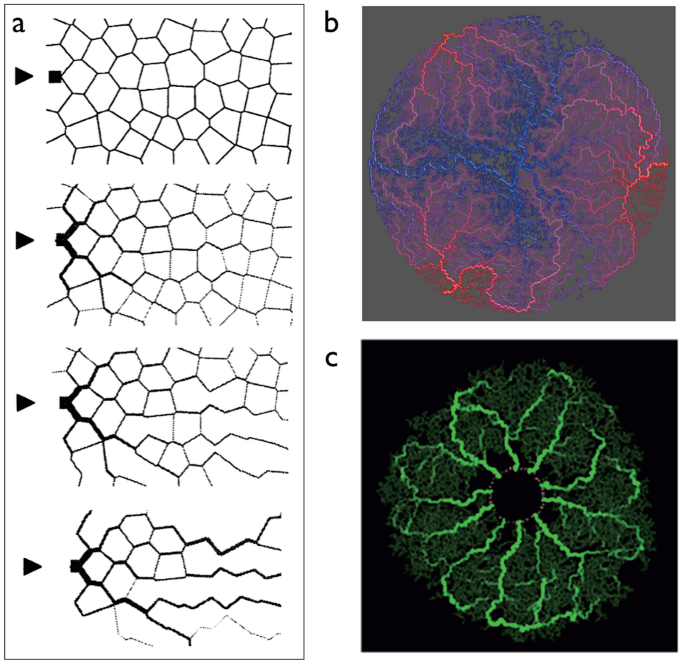

Fig. 3 Models of vascular remodeling. **(a)** Model proposed by Hisao Honda[33]. The model uses the principle that vessel with more flow becomes thicker. **(b)** Similar rule can generate intermingled pattern or arterial-venous trees[34]. **(c)** A model of retina vasculature remodeling[35]. Since arterial input and venous output is very close, there must be some mechanism to prevent shunt formation[36].

Experimental test of the models can be done using molecular and synthetic approach. Arterial-venous differentiation is regulated by Ephrin-Eph system[41)~43)]. Pericytes also plays a role in remodeling process of retina vasculature[44)]. Modification of these factors can be a tool to experimentally verify the theoretical models. Recently it becomes possible to generate perfusable capillary network inside microdevice[45)46)], that can also be a tool to directly induce remodeling process *in vitro*. In our laboratory we successfully generate perfusable vascular network in microfluidic device[47)]. Interestingly, the mechanism of pattern formation in the microdevice seems to be different from those proposed previously (data not shown).

In all three cases, at first a minimal model to explain the fundamental part of the pattern formation is formulated, which is later followed by large-scale computational models to explain various other aspects. Minimal models and large-scale models have different roles-minimal model is necessary to understand the mechanism, and large-scale model is useful in discovering a new aspect of the phenomenon. In the future, various minimal models that represent part of the large-scale models will be utilized to truly understand the model behaviors *in silico* and *in vivo*.

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(References with numbers in bold are listed as particularly important ones for readers.)

（和文抄録）

血管パターン形成の理論モデル

九州大学大学院医学研究院 系統解剖学分野

三　浦　　岳

血管のパターン形成は血管生物学の分野で盛んに研究されている．古典的には，血管のパターン形成は vasculogenesis, angiogenesis, remodeling の 3 つのカテゴリーに分類される．血管のパターン形成の数理モデルの研究は，応用数学者によって実験的研究とは比較的独立に研究されてきたため，これまで生物学者にはあまりよく理解されていなかった．この総説では，古典的な血管のパターン形成の数理モデルの直感的な説明を述べ，この分野の将来展望について概観する．

キーワード：血管パターン形成，理論モデル