

# Development of Maximized Total Capillary Surface: the quarter power scaling law from developmental biology perspective

Dawei Hong  
Dept. of Computer Science  
Rutgers University  
Camden, NJ 08102 USA  
dhong@camden.rutgers.edu

Daniel Shain  
Dept. of Biological Science  
Rutgers University  
Camden, NJ 08102 USA  
dshain@camden.rutgers.edu

Shushuang Man  
Dept. of Math./Computer Science  
Southwest Minnesota State University  
Marshall, MN 56258 USA  
mans@southwestmsu.edu

Joseph V. Martin  
Dept. of Biological Science  
Rutgers University  
Camden, NJ 08102 USA  
jomartin@camden.rutgers.edu

**Abstract**—Quarter-power scaling of biological features with body mass is commonly observed in a variety of organisms and is considered a universal law in biology. The origin of the quarter-power scaling law has been proposed to be a universal requirement of a maximized hierarchical network for distributing materials (e.g., oxygen and nutrients) in any organism. We propose a mathematical model for the development of a maximized total capillary surface. This model quantitatively demonstrates how body mass is related to the biological information controlling development of capillaries under the condition that the maximization of total capillary surface area is subject to the minimization of the informational complexity.

**Keywords:** Quarter power scaling law; Modeling of development of capillaries; Probabilistic counting

## I. INTRODUCTION

Kleiber’s law of allometric scaling states that the basal metabolic rate of an organism is proportional to its mass to the  $\frac{3}{4}$  power (Kleiber, 1932; Schmidt-Nielsen, 1984). Empirical data for numerous biological variables in a large variety of animals and plants fit allometric scaling relationships which are simple multiples of a quarter-power (Schmidt-Nielsen, 1984; cf. Brown *et al.* 2002; West and Brown 2005). West, Brown and Enquist (1997, 1999) proposed a model to explain the ubiquitous quarter-power allometric scaling relationship. The spirit of the model can be summarized as follows. Let  $A$  and  $M$  denote respectively the total capillary surface area and the mass in average over all individuals of a given species. Then for that species there is a constant  $M_0$  such that

$$A = M_0 \cdot M^{\frac{3}{4}} \quad (1)$$

Furthermore,  $A$  is directly related to variety of biological functions, such as metabolic rate. Theoretical predictions of the West-Brown-Enquist model have been shown to closely

match observed data for mammals and birds (Savage *et al.* 2004), plants (Niklas and Enquist, 2001) and other organisms (Damuth 2001; Gillooly *et al.* 2001, 2002; Enquist *et al.* 2003). With (1) a universal equation for growth was obtained (see equation (5) in West *et al.* 2001). Though it is similar to the classical sigmoidal curve of von Bertalanffy (cf. Reiss 1989), this universal equation is directly derived from the cellular parameters that govern growth, and thus, sets a link between growth and fundamental cellular parameters.

A key step in the derivation of (1) is based on that animals have evolved so as to maximize total capillary surface area subject to various physical and geometric constraints (p. 1679 West *et al.* 1999). In the following, we will use the term “maximized total capillary surface” to mean “maximized total capillary surface area subject to various physical and geometric constraints”. The agency for evolution is development (cf. Raff 2000; Raff and Sly 2000; Wilkins 2002). That any animal has evolved a maximized total capillary surface implies that there is an essential mechanism shared by all animals for developing such a surface. Beneficial developmental mechanisms are “re-used” by different species; and hence, there should be an underlying mathematical model that captures such a mechanism. Moreover, since this developmental mechanism is genetically programmed, the model should also show how the mechanism is related to the developmental information for capillaries. We propose a model for the mechanism, which demonstrates a quantitative relation between body mass and the developmental information for capillaries. Our attempt is in theory to uncover a relation between the quarter power scaling law and its genetic basis.

The genes associated with early development of human pulmonary veins (Hall *et al.* 2002) or murine blood vessels (Argraves and Drake 2005), are not well characterized, but if

we consider capillary development from a theoretical viewpoint then it is possible to propose a mathematical model for the process. Capillary development essentially follows the body plan, i.e., the biological information co-opted in the embryo. Beginning with this, we form the proposed model by three components as follows.

- (i) The reflection of the body plan on cell lineage paths is modeled by a combinatorial structure, a forest of binary trees, that describes how cell lineage paths follow physical and geometric constraints;
- (ii) A cell lineage path is viewed as a sequence of gene expression profiles. Taking variation in gene expression into account, we model cell lineage paths by a stochastic process with independent increments;
- (iii) With a stochastic process and combinatorial structure, we quantify the biological information for capillary development by a numerical parameter  $0 < q < 1$ . Here,  $1 - q$  is the percentage of cell lineage paths that can be viewed as randomly generated via variation in gene expression. The detail is presented in Subsection II-C.

Assume that for a given kind of animal, the growth of each capillary takes the same (average) number  $(T + 1)$  of cell cycles. In accordance with the West-Brown-Enquist model, we use  $A$  to denote the area of maximized total capillary surface. Let  $A_0$  denote the average amount that each capillary cell contributes to  $A$ .

*Theorem 1:*

$$A = A_0 \cdot \left( \frac{1}{1 - q} \right)^{-T}$$

and consequently, by (1)

$$M = \left( \frac{A_0}{M_0} \right)^{\frac{4}{3}} \cdot \left( \frac{1}{1 - q} \right)^{-\frac{4T}{3}}$$

A proof of this theorem is in Section III. The theorem predicts a quantitative relation between body mass and variation in gene expression in growth of capillaries. For example, it shows how additional genetic information to control growth of capillaries implies increasing of body mass.

## II. DESCRIPTION OF THE MODEL

### A. The constraints

The material distribution system in an animal (or plant) is described as a space-filling fractal-like structure with terminal branches (e.g., capillaries) which supply mostly distinct microscopic regions of tissue (cf. West *et al.* 1997). In our proposed model, the term ‘‘a cell cycle’’ is used as a time unit, assuming that, for a kind of animal, a division of capillary cell always takes the same amount  $s$  of time. The growth of a capillary is monitored at times  $s, 2s, \dots, (T + 1)s$ , resulting in a CLP. If there were no constraints, then in  $(T + 1)$  cell cycles all CLP would form a complete binary tree with height  $(T + 1)$ . Here, following the convention in combinatorics, the root of a complete binary tree is at level 0, its two children are the two

nodes at level 1; in general, for an internal node at level  $t$ , its two children are two nodes at level  $(t + 1)$ ; and the number of levels is the height of the binary tree. A complete binary tree with height  $(T + 1)$  has totally  $\sum_{t=0}^T 2^t = 2^{T+1} - 1$  nodes. The differentiation and growth of any capillary is subject to constraints. For example, the growth of a capillary residing in muscle must be synchronized with muscle growth. As a result, instead of a complete binary tree, an incomplete binary tree is obtained when the growth of a capillary is monitored over  $(T + 1)$  cell cycles. By an incomplete binary tree we mean a directed tree such that its root is at level 0, and for  $0 \leq t < T$ , an internal node at level  $t$  has in some cases, one (instead of two) child nodes at level  $(t + 1)$ . Figure 1 illustrates an incomplete binary tree. Each path in this incomplete binary tree represents CLP in the growth of a capillary. As an example, the incomplete binary tree in Figure 1 has eight CLP, each of which is a sequence of nine capillary cells. For capillaries residing in different parts of the body, constraints are not necessarily the same, and hence, different incomplete binary trees would result.

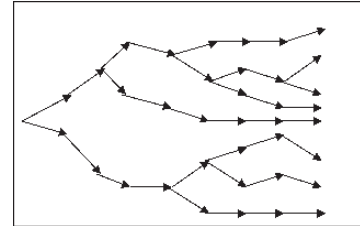


Fig. 1. Structure of an incomplete binary tree. Eight CLP are depicted, each of which is a sequence of nine capillary precursor cells. For instance, in the CLP on the top, of the nine cells, the second is the result of the division of the first one; the third may either be the result of the division of the second that produced two children one of which died, or the older second. This incomplete binary illustrates the growth of a capillary made of eight capillary cells (each CLP contributes a cell).

Considering all capillaries in the body of an animal, we have a set of incomplete binary trees, each branch of which reflects the constraints on the growth of one capillary and collectively forms a forest ( $\mathcal{F}$ ). This forest is the combinatorial structure used to reflect the physical and geometric constraints on CLP in capillary growth, i.e. the reflection of the body plan in capillary development.

However, with  $\mathcal{F}$  alone we can not answer the key question to our proposed model: How is the total capillary surface maximized? Indeed, given all details of  $\mathcal{F}$ , a value of the total capillary surface area  $A$  can be calculated under the assumption that each CLP contributes the same amount to  $A$ ; yet the question why the value of  $A$  is maximized remains. In next subsection, we examine CLP at a genetic level.

### B. The CLP

At a cellular level, each CLP appears the same. (Recall that each of the eight CLP in Figure 1 is a sequence of nine capillary cells.) However, gene expression profiles of capillary

cells can detect differences among CLP. The gene expression profiles of all successive cells along a CLP form a sequence. In the following, we call such a sequence GEP. Each CLP in Figure 1 is a GEP, a sequence of nine gene expression profiles. Variation in gene expression can be viewed as random (Cheung and Spielman 2002), since, for example, allelic variation in gene expression is commonly found in the human genome (Lo *et al.* 2003). For development of capillaries, the randomness of variation in gene expression is as follows. There are different GEP, and for CLP, the GEP (as the CLP) has a random component. Thus, from a mathematical viewpoint, all CLP can be modeled by a stochastic process.

Stochastic differential equation (SDE) is a mathematical framework that provides a systematic way to manipulate stochastic processes. In general, two steps are required to apply SDE to modeling of the dynamics of gene expression. By definition, a SDE transforms a function into a stochastic process, and the transform is carried out under the weak topology built upon the Borel measure on a finite interval of  $\mathbf{R}$  and the standard Brownian filtration (cf. Steele 2000). After setting and solving a SDE as the first step, the second step is to apply rule(s) to choosing paths in the stochastic process that represent the dynamics of gene expression. Recently, Chen *et al.* (2005) demonstrates that for *Saccharomyces cerevisiae* the dynamics of gene expression over cell cycles can be well captured by a special SDE with the AIC (a classic result in control theory) applied as the rule to choose paths. To model the development of capillaries, our approach is to combine the two steps into one by defining a class of discrete stochastic processes. This definition follows from an insight into SDE. For SDE in a family, the solution is a continuous stochastic process with independent increments. For example, any SDE,  $dX_t = f_t dt + g_t dB_t$  where  $f_t$  and  $g_t$  are differentiable functions on  $[0, T]$ , belongs to the family. In the SDE used in Chen *et al.* 2005,  $f_t$  is specified for *Saccharomyces cerevisiae* and  $g_t$  is a constant. We consider discrete stochastic process  $\mathcal{C}$  with independent increments over  $(T + 1)$  generations. The independence is used to capture the randomness of variation in gene expression; in the meantime, the specification required for a particular kind of animal is treated at abstract level. The eight CLP in Figure 1 are read as eight paths in  $\mathcal{C}$ .

Recall that the reflection of the body plan on the CLP in the development of capillaries is modeled by a forest  $\mathcal{F}$  of incomplete binary trees. All CLP read as GEP are modeled by a discrete stochastic process with independent increments over  $(T + 1)$  generations, one generation for each cell cycle. Thus, we model the development of capillaries of an individual using paths in the stochastic process to fill out  $\mathcal{F}$ . Using eight appropriate paths in the stochastic process to fill out the tree in Figure 1 illustrates the growth of one capillary at a site.

### C. Randomness in development of capillaries

To complete the proposed model, we quantify the biological information for the development of capillaries. Our approach is motivated by a rather philosophical thought, namely that randomness is the most fundamental force behind evolution,

and thus, it should be an important factor in development, the agency for evolution. As discussed in the previous subsection, in the development of capillaries, randomness is expressed via GEP which will be accordingly modeled by a discrete stochastic process with independent increments. GEP can be viewed as the result of the biological information that controls the development of capillaries. We will also use GEP to quantify the biological information. To confirm this idea, let us look at how the biological information is conveyed. The mean to convey this biological information is molecular communication. Recently, it is revealed that molecular communication in the nature is stochastic (Springer and Paulsson 2006). A proposed model of molecular communication by Zhou *et al.* (2005) is SDE. As pointed by Springer and Paulsson (2006), molecular communication has two components: deterministic and stochastic (noise-driven). Thus, we can quantify biological information by the deterministic component of the molecular communication that conveys the information.

For the development of capillaries, the deterministic component results in a subset of GEP that do commit to this development in the following way: for any GEP, there exists GEP in this subset so that the former (GEP) shares a prefix with the later, and the suffix of the former is a variation (in gene expression) of the suffix of the later. For example, the second path (from top to bottom) in Figure 1 can be considered in the subset, since the third path can be viewed as generated from it (at the last cell cycle); however, the first path is not in the subset, since along this path there is only one child cell after most cell cycles, which indicates that the biological information has more control on that path to meet the constraint on the development of capillaries. Given a kind of animal, let us consider the minimum of all possible such subsets of GEP. Then the size of this minimum subset quantifies the biological information for the development of capillaries: the large the size is the more information there is. We assume that during evolution any kind of animal has found the minimum subset; and to this extent, we claim that the informational complexity for the development of capillaries is minimized. To formally describe this, we introduce notations that also will be used in the mathematical formulation of the proposed model in Section III.

Let  $\Omega$  denote a  $(T + 1)$ -dimensional finite set. We denote  $\omega \in \Omega$  by  $\omega = (\omega_1, \dots, \omega_{T+1})$ . Let  $\mu$  be the uniform distribution on  $\Omega$ .  $\omega$  represents CLP in the development of capillaries. That  $\mu$  is uniform indicates that each CLP as a sequence of capillary cells is equally likely to be used by an individual. We define a process  $\mathcal{C}$  on the probability space  $(\Omega, \mu)$ :

$$\mathcal{C}(t, \omega) : \{1, \dots, (T + 1)\} \times \Omega \mapsto V \quad (2)$$

satisfying that for  $1 \leq t \leq (T + 1)$ , there is a function  $C_t : \Omega_t \mapsto V$  such that  $\mathcal{C}(t, \omega) = C_t(\omega_t)$  for all  $\omega \in \Omega$ . Process (2) proceeds through cell cycles marked by  $1, \dots, (T + 1)$ . In a path  $\omega$  in  $\mathcal{C}$ , at the  $t$ th cell cycle,  $\omega_t$  represents the cell and  $C_t(\omega_t)$  is the gene expression profile read from  $\omega_t$ . That is,  $(C_1(\omega_1), \dots, C_{T+1}(\omega_{T+1}))$  is the sequence of gene expression

profiles (GEP) for the CLP represented by  $\omega$ , and accordingly,  $V$  is the set of all possible GEP.

We call paths  $\omega$  and  $\omega'$  in  $\mathcal{C}$  companions, if for some  $1 \leq t \leq T$ ,  $\omega_s = \omega'_s$  for all  $1 \leq s \leq (t+1)$  and  $\omega_s \neq \omega'_s$  for all  $(t+2) \leq s \leq (T+1)$ , and if the subsequence  $(C_{t+2}(\omega_{t+2}), \dots, C_T(\omega_T))$  is either empty, or is a variation (in gene expression) of the subsequence  $(C_{t+2}(\omega'_{t+2}), \dots, C_T(\omega'_T))$ . Notice that by definition a path is always a companion of itself. A subset of  $\Omega$  is said to be feasible if every  $\omega \in \Omega$  has a companion in this subset. Let  $\Gamma_{\min}$  be the feasible subset with minimum size. And let  $q = \mu(\Gamma_{\min})$ . Notice that since  $\mu$  is uniform, each  $\omega$  is assigned with equal probability  $|\Omega|^{-1}$ , and thus,  $q = \mu(\Gamma_{\min})$  counts the percentage of GEP in  $\Gamma_{\min}$  over all GEP.

In next section, we will define a class of stochastic processes, namely adaptable processes, so that the discrete version of the solution of SDE in Chen *et al.* 2005 belongs to it. Then we apply adaptable process to the development of capillaries, proving Theorem 1.

### III. MATHEMATICAL FORMULATION

To characterize how the probabilistic distribution on all GEP progresses over cell cycles, we let for  $1 \leq t \leq (T+1)$ ,  $[\omega_1, \dots, \omega_t] \stackrel{\text{def}}{=} \{\omega' \in \Omega \mid \omega'_s = \omega_s, s = 1, \dots, t\}$ , and let  $\Delta_t$  be the union of all  $[\omega_1, \dots, \omega_t]$ , i.e.  $\cup[\omega_1, \dots, \omega_t]$ . That is,  $\Delta_t$  is obtained by re-grouping the elements in  $\Omega$ . (Thus,  $\Delta_t = \Omega$  for all  $1 \leq t \leq (T+1)$ .) And accordingly, we let  $\mu_t$  denote the probability measure on  $\Delta_t$  induced by  $\mu$  in the usual way. Then  $(\Delta_t, \mu_t)$  is a probability space. Notice that  $\Delta_t$  can be thought as a partition on  $\Omega$ , and  $\Delta_{t+1}$  is refinement of  $\Delta_t$ . This viewpoint will be used shortly.

We recall that a mass transportation from  $(\Delta_t, \mu_t)$  to  $(\Delta_{t+1}, \mu_{t+1})$  is defined as a probability measure on  $\Delta_t \times \Delta_{t+1}$  so that  $\mu_t$  and  $\mu_{t+1}$  are respectively the first and second marginal (cf. Rachev and Rüschendorf, 1998). Intuitively, a mass transportation pushes  $\mu_t$  forward to  $\mu_{t+1}$ . Given  $(\Delta_t, \mu_t)$  and  $(\Delta_{t+1}, \mu_{t+1})$ , there can be many mass transportations. We are interested in a particular one  $\tau_t$  directly induced by  $\mu$  as follows. For  $(\omega^{(t)}, \omega^{(t+1)}) \in \Delta_t \times \Delta_{t+1}$

$$\tau_t((\omega^{(t)}, \omega^{(t+1)})) \stackrel{\text{def}}{=} \mu(\omega^{(t+1)}) \quad (3)$$

if for some  $(\omega_1, \dots, \omega_t, \omega_{t+1}, \dots, \omega_T) \in \Omega$ ,  $\omega^{(t)} \in [\omega_1, \dots, \omega_t]$  and  $\omega^{(t+1)} \in [\omega_1, \dots, \omega_t, \omega_{t+1}]$ ; otherwise, zero. It is straightforward to verify that  $\tau_t$  is a mass transportation from  $(\Delta_t, \mu_t)$  to  $(\Delta_{t+1}, \mu_{t+1})$ . Let  $\Xi \stackrel{\text{def}}{=} (\Delta_1 \times \Delta_2) \times \dots \times (\Delta_t \times \Delta_{t+1}) \times \dots \times (\Delta_T \times \Delta_{T+1})$ . The probability measure  $\mu$  on  $\Omega$  ultimately determines a joint probability measure on  $\Xi$ . Let  $\tau$  denote this probability measure. We call  $(\Xi, \tau)$  the increment space of  $\mathcal{C}$ .

*Definition 2:* A process  $\mathcal{C}$  is said to be adaptable, if its increment space  $(\Xi, \tau)$  is a product probability space with  $\tau = \prod_{t=1}^T \tau_t$ .

This definition follows from an insight into Ito's integral, the major tool for solving SDE. In the discrete case, Ito's integral becomes martingale transform. So, instead of the

standard Brownian filtration, we use an increasing chain of partitions on  $\Omega$ ,  $\Delta_1 \subset \Delta_2 \subset \dots \subset \Delta_{T+1}$ , together with  $\mu_t$  to form a discrete filtration, and then with this discrete filtration we use  $\tau_t$  to carry out a martingale transform. There is no regularity restriction on how  $\Delta_t$  are formed so that the solution of any SDE  $dX_t = f_t dt + g_t dB_t$  where  $f_t$  and  $g_t$  are differentiable functions on  $[0, T]$  has its discrete version representable by an adaptable process.<sup>1</sup> It is helpful to see what an adaptable process implies in biological terms. We use the proposed model as an example.  $\omega = (\omega_1, \dots, \omega_T)$  represents CLP, and  $(C_1(\omega_1), \dots, C_T(\omega_T))$  is the GEP for the CLP. Thus,  $\mu([\omega_1, \dots, \omega_t])$  is the probabilistic measure of CLP that share the same prefix  $(C_1(\omega_1), \dots, C_t(\omega_t))$ . Therefore,  $\tau_t$  in probabilistic terms captures the change from  $(C_1(\omega_1), \dots, C_t(\omega_t))$  to  $(C_1(\omega_1), \dots, C_t(\omega_t), C_{t+1}(\omega_{t+1}))$ . As a sequence of gene expression profiles  $(C_1(\omega_1), \dots, C_t(\omega_t), C_{t+1}(\omega_{t+1}))$  may well depend on  $(C_1(\omega_1), \dots, C_t(\omega_t))$ . However, when all changes (from  $(C_1(\omega_1), \dots, C_t(\omega_t))$  to  $(C_1(\omega_1), \dots, C_t(\omega_t), C_{t+1}(\omega_{t+1}))$ ) are considered, they are stochastically independent which is expressed by  $\tau = \prod_{t=1}^T \tau_t$ . This idea was used for the proposed model in Chen *et al.* 2005 (cf. Subsection 2.1 therein). Here, we mathematically formulate it in a general way.

We apply adaptable process to the development of capillaries. A path  $\omega$  in  $\mathcal{C}$  is said to fill out a path in a tree in  $\mathcal{F}$ , if for all  $1 \leq t \leq (T+1)$ ,  $\omega_t$  represents the  $t$ th node in the path in this tree. For example, in case of  $T = 8$ ,  $\omega$  fills out the top path in Figure 1 if  $\omega_t$  represent the nine nodes from left to right, respectively. A process  $\mathcal{C}$  is said to be with respect to  $\mathcal{F}$ , if it satisfies the following two conditions: (i) every path in  $\Omega$  fills out exactly one path in one tree in  $\mathcal{F}$ , and each path in a tree in  $\mathcal{F}$  is filled out by a path in  $\Omega$ ; and (ii) for any two paths  $\omega$  and  $\omega'$  in  $\Omega$  and any  $1 \leq t \leq (T+1)$ , if  $\omega_t$  and  $\omega'_t$  represent the same node in a path in a tree in  $\mathcal{F}$  then  $\omega_t = \omega'_t$ .

*Definition 3:* A process  $\mathcal{C}$  is said to be a capillary development process, if it is adaptable and is with respect to  $\mathcal{F}$ . For a given kind of animal, we assume that the capillary development process  $\mathcal{C}$  is a fixed one.

The method used to prove Theorem 1 follows from the probabilistic counting principle. The idea behind the principle can be simply illustrated. Given a set  $\Omega$  which has a defined mathematical structure, we are asked to find the size  $|\Omega|$  of the set. In principle, the problem can be solved as follows. We impose a uniform probabilistic distribution on  $\Omega$  so that each element in the set is assigned with the same probability  $p$ . Then with the mathematical structure we show that  $p \geq \epsilon$  for some  $\epsilon > 0$ , concluding  $|\Omega| \leq \frac{1}{\epsilon}$ . Examples of the utility of probabilistic counting in problem solving can be found in Alon *et al.* 1991.

*Proof of Theorem 1:* Given a capillary development process  $\mathcal{C}$ , we consider its increment space  $(\Xi, \tau)$ . Recall definition

<sup>1</sup>A mathematical proof for this statement is to compare all constructions completed thus far with the three steps in defining Ito's integral (cf. chapter 3 of Steele 2000).

of  $\tau_t$  in (3) and definition of  $\Gamma_{\min}$  in Subsection II-C. Let

$$H_t \stackrel{\text{def}}{=} \left\{ (\omega^{(t)}, \omega^{(t+1)}) \in \Delta_t \times \Delta_{t+1} \mid \omega^{(t+1)} \in \Gamma_{\min} \right\}$$

By definition we have  $\tau_t(H_t) = q$ . In the meantime,  $H_t$  can be read as an event: find a segment  $(\omega_t, \omega_{t+1})$  that belongs to a path  $\omega \in \Gamma_{\min}$ . Let  $\widetilde{H}_t$  denote the complement event of  $H_t$ . Then  $\tau_t(\widetilde{H}_t) = 1 - q$ . Notice that both  $H_t$  and  $\widetilde{H}_t$  are events in the probability space  $(\Delta_t \times \Delta_{t+1}, \tau_t)$ . Let  $\widetilde{H}_* \stackrel{\text{def}}{=} \widetilde{H}_1 \cap \widetilde{H}_2 \cap \dots \cap \widetilde{H}_T$ . Then  $\widetilde{H}_*$  is an event in the probability space  $(\Xi, \tau)$ . Since  $\mathcal{C}$  is a capillary development process,  $(\Xi, \tau)$  is a product space with  $\tau = \prod_{t=1}^T \tau_t$ . Thus,

$$\tau(\widetilde{H}_*) = \prod_{t=1}^T \tau_t(\widetilde{H}_t) = (1 - q)^T \quad (4)$$

Now, let us conduct a trial as follows. Randomly and uniformly, choose a path  $\omega' \in \Omega$ ; and then for  $t = 1$  to  $T$ , check if the event  $H_t$  happens, i. e., if there is  $\omega \in \Gamma_{\min}$  such that  $\omega'_s = \omega_s$ ,  $s = t$  and  $t + 1$ . We succeed in the trial if  $H_t$  happens for some  $t$ ; otherwise, we would fail. Since the size of  $\Omega$  is  $|\Omega|$ ,  $\omega'$  is chosen with probability  $\frac{1}{|\Omega|}$ . On the other hand, by (4) the probability of failure in the trial is  $(1 - q)^T$ .

By definition any  $\omega' \in \Omega$  has a companion in  $\Gamma_{\min}$ , and hence,  $H_t$  must happen for some  $t$ ,  $1 \leq t \leq T$ . That is, in the trial we never fail, which means that  $\frac{1}{|\Omega|} > (1 - q)^T$  yielding  $|\Omega| < (1 - q)^{-T}$ . Therefore, the maximum of  $|\Omega|$  is  $\lfloor (1 - q)^{-T} \rfloor$  which can be taken as  $(1 - q)^{-T}$ . So far, we have shown that the maximum number of CLP in the growth of capillaries is  $(1 - q)^{-T}$ .

The theorem follows from that (i) each CLP results in one capillary cell at the  $(T + 1)$ st cell cycle, and (ii) the average amount that each capillary cell contributes to the total capillary surface is  $A_0$ . ■

#### REFERENCES

- Alon, N., J. H. Spencer, J. H. Erdős, P., 1991, *The Probabilistic Method*. Wiley.
- Argaves, W. S., Drake, C. J., 2005, Gene critical to vasculogenesis as defined by systemic analysis of vascular defects in knockout mice. *The Anatomical Record* **286A**, 875-884.
- Brown, J. H., Gupta, V. K., Li, B-L., Milne, B. T., Restrepo, C., West, G. B., 2002, The fractal nature of nature: power laws, ecological complexity and biodiversity. *Proceedings of the Royal Society B* **357**, 619-626.
- Chen, K-C., Wang, T-Y., Tseng, H-H., Huang, C-Y. F., Kao, C-Y., 2005, A stochastic differential equation model for quantifying transcriptional regulatory network in *Sacharomyces cerevisiae*. *Bioinformatics* **21**, 2883-2890.
- Cheung, V. G., Spielman, R. S., 2002, The genetics of variation in gene expression. *Nature Genetics Supplement* **32**, 522-525.
- Damuth, J., 2001, Scaling of growth: Plants and animals are not so different. *Proceedings of National Academy of Sciences USA* **98**, 2113-2114.
- Enquist, B.J., Economo, E.P., Huxman, T.E., Allen, A.P., Ignace, D.D., Gillooly, J.F., 2003, Scaling metabolism from organisms to ecosystems. *Nature* **423**, 639-642.
- Ernest, S.K.M., Enquist, B.J., Brown, J.H., Charnov, E.L., Gillooly, J.F., Savage, V., White, E.P., Smith, F.A., Hadly, E.A., Haskell, J.P., Lyons, S.K., Maurer, B.A., Niklas, K.J., Tiffney, B., 2003, Thermodynamic and metabolic effects on the scaling of production and population energy use. *Ecology Letters* **6**, 990-995.
- Gillooly, J.F., Brown, J.H., West, G.B., Savage, V.M., Charnov, E.L., 2001, Effects of size and temperature on metabolic rate. *Science* **293**, 2248-2251.
- Gillooly, J.F., Charnov, E.L., West, G.B., Savage, V.M., Brown, J.H., 2002, Effects of size and temperature on developmental time. *Nature* **417**, 70-73.
- Hall, S. M., A. A. Hislop, A. A., Haworth, S. G., 2002, Origin, differentiation, and maturation of human pulmonary veins. *American Journal of Respiratory Cell and Molecular Biology* **26**, 333-340.
- Kleiber, M., 1932, Body size and metabolism. *Hilgardia* **6**, 315-353.
- Lo, H. S., Wang, Z., Hu, Y., Yang, H. H., Gere, S., Buetow, K. H., Lee, M. P., 2003, Allelic variation in gene expression is common in the human genome. *Genome Research* **13**, 1855-1862.
- Niklas, K. J., Enquist, B. J., 2001, Invariant scaling relationships for interspecific plant biomass production rates and body size. *Proceedings of National Academy of Sciences USA* **98**, 2922-2927.
- Rachev, S. T., Rüschemdorf, L., 1998, *Mass Transportation Problems* Volume I: Theory and Volume II: Applications. Springer-Verlag.
- Raff, R. A., 2000, Evo-devo: the evolution of a new discipline. *Nature Reviews Genetics* **1**, 74-79.
- Raff, R. A., Sly, B. J., 2000, Modularity and dissociation in the evolution of gene expression territories in development. *Evolution and Development* **2:2**, 102-113.
- Reiss, M. J., 1989, *The Allometry of Growth and Reproduction*. Cambridge University Press.
- Schmidt-Nielsen, K., 1984, *Scaling: Why is Animal Size so Important?* Cambridge University Press, New York.
- Springer, M., Paulsson, J., 2006, Harmonies from noise. *Nature* **439** 27-28.
- Steele, J. M., 2000, *Stochastic Calculus and Financial Applications*. Springer.
- West, G. B., Brown, J. H., eds. 2000, *Scaling in Biology*. Sante Fe Institute studies in the science of complexity, Oxford University Press.
- West, G. B., Brown, J. H., 2005, The origin of allometric scaling laws in biology from genomes to ecosystems: toward a quantitative unifying theory of biological structure and organization. *The Journal of Experimental Biology* **208**, 1575-1592.
- West, G. B., Brown, J. H., Enquist, B. J., 1997, A general model for the origin of allometric scaling laws in biology. *Science* **276**, 122-126.
- West, G. B., Brown, J. H., Enquist, B. J., 1999, The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* **284**, 1677-1679.
- West, G. B., Brown, J. H., Enquist, B. J., 2001, A general model for ontogenetic growth. *Nature* **413**, 628-631.
- Wilkins, A. S., 2002, *The Evolution of Developmental Pathways*. Sinauer.
- Zhou, T., Chen, L., Aihara, K., 2005, Molecular communication through stochastic synchronization induced by extracellular fluctuations. *Physical Review Letters* **95** 178103.