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Heterogeneity of cells may explain allometric scaling of metabolic rate

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ABSTRACT

The origin of allometric scaling of metabolic rate is a long-standing question in biology. Several models have been proposed for explaining the origin; however, they have advantages and disadvantages. In particular, previous models only demonstrate either two important observations for the allometric scaling: the variability of scaling exponents and predominance of 3/4-power law. Thus, these models have a dispute over their validity. In this study, we propose a simple geometry model, and show that a hypothesis that total surface area of cells determines metabolic rate can reproduce these two observations by combining two concepts: the impact of cell sizes on metabolic rate and fractal-like (hierarchical) organization. The proposed model both theoretically and numerically demonstrates the approximately 3/4-power law although several different biological strategies are considered. The model validity is confirmed using empirical data. Furthermore, the model suggests the importance of heterogeneity of cell size for the emergence of the allometric scaling. The proposed model provides intuitive and unique insights into the origin of allometric scaling laws in biology, despite several limitations of the model.

1. Introduction

Metabolic processes are essential for physiological functions and responsible for maintaining life (Takemoto, 2012; Takemoto and Oosawa, 2012). The relationship between metabolic rate B and body mass M is an important and interesting topic of scientific inquiry not only for researchers in the field of basic biology but also for investigators in ecology and medical research, and it is well known to approximately obey a power law (West et al., 2002; Brown et al., 2004): $B \propto M^{\gamma}$. This allometry is positioned as a significant equation in both biology and ecology because it is useful for understanding and for estimating the energy metabolism, lifespan (Speakman, 2005), and animal space use (Jetz et al., 2004); in particular, determination of the scaling exponent γ is a long-standing question.

A pioneering study includes the surface law found by Rubner in the 1880s (White and Seymour, 2003); in particular, Rubner reported that metabolic rate is proportional to $M^{2/3}$ in mammals. The Rubner's surface law is immediately derived when assuming simple geometric and physical principles: metabolic rate (e.g., heat production rate) is proportional to the rate of energy (e.g., heat) dissipated through body surface because of homeostasis.

Contrary to the prediction from the surface law, in 1932, Kleiber proposed that metabolic rate is proportional to $M^{3/4}$ (White and Seymour, 2003; West et al., 2002; Speakman, 2005; Brown et al., 2004). Further studies have confirmed that the Kleiber's (i.e., 3/4-power) law is predominant at least in plants and animals (reviewed in Savage et al., 2004): this allometric scaling is observed in wide-ranging organisms (i.e., microorganisms to elephants).

West et al. (1997) have proposed a model (West–Brown–Enquist (WBE) model) for explaining the origin of the 3/4-power law. This model assumes that oxygen and nutrients are transported through space-filling fractal networks of branching tubes, in which the number of capillaries (leaves in the case of plants) is proportional to metabolic rate. Since the WBE model clearly illustrates the Kleiber's law, it is frequently used for understanding the allometric scaling.

In addition to this, further studies have proposed several alternative models based on the fourth dimension of life (West et al., 1999), transport networks (Banavar et al., 1999), and quantum metabolism (Demetrius and Tuszynski, 2010).

However, these models have several limitations (e.g., Price et al., 2012 have carefully evaluated the WBE model using empirical data). In particular, Kozłowski and Konarzewski (2004) have questioned the universality of the 3/4-power law. In fact, several studies suggest that the scaling exponent γ is variable. For example, White and Seymour (2003) have reported that metabolic rate is proportional to $M^{2/3}$ in mammals when considering body temperature, digestive state, and phylogeny. Darveau et al. (2002)

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have illustrated that the approximately 3/4-power law results from the sum of the influences of multiple contributors to metabolism and control (i.e., the sum of allometric relationships observed in a number of biological processes). Reich et al. (2006) found that a linear relationship between the rate of respiratory metabolism and body mass (i.e., $B \propto M$) is observed in plants although Enquist et al. (2007) have refuted this conclusion. Similarly, the observed similar mean mass-specific metabolic rates across life's major domains (Makarieva et al., 2008) also implies that $B \propto M$. To explain the variability of the scaling exponent, however, the WBE model can be modified (Price et al., 2007; Kolokotrones et al., 2010).

Of particular interest is the fact that the scaling exponent varies according to cell size (Kozłowski et al., 2003; Starostová et al., 2009). Thus, Kozłowski et al. (2003) have proposed a simple model (Kozłowski–Konarzewski–Gawelczyk (KKG) model) based on cell size, inspired by the fact that a large part of standard metabolic costs are spent preserving ionic gradients on cell membranes (Szarski, 1983; Porter and Brand, 1993). This model considers an extension of the Rubner's surface law: a hypothesis that metabolic rates are determined by total surface area of cells rather than body surface. The KKG model can explain the variability of the scaling exponent; especially, the exponent can fall within the range between 2/3 and 1. For example, $B \propto M^{2/3}$ when cell size is proportional to body size. On the other hand, $B \propto M$ when cell size is independent from body size. The variability of the scaling exponent has already well known in terms of geometry (Okie, 2013; Hirst et al., 2014).

Brown et al. (2005) have argued against the KKG model. Since cell size is almost independent from body size, as explained by Kozłowski et al. (2003), the KKG model suggests $B \propto M$, indicating that it contradicts the predominance of the 3/4-power law (Savage et al., 2004).

Is the KKG model or a hypothesis that the total surface area determines metabolic rate not really useful for understanding the allometric scaling law? In this study, we propose a simple geometry model, an extended KKG model, and show approximately 3/4-power law can be also emerged from this hypothesis by considering the concept of fractal-like (hierarchical) organization of the WBE model. This result suggests that the hypothesis is evidently useful for understanding allometric scaling of metabolic rate. Moreover, our model explains both validity of the scaling exponent and ubiquity of the 3/4-power laws, and it suggests that the allometric scaling of metabolic rate is affects by cell size distributions, rather than cell sizes.

2. A geometry model

The KKG model assumes that organisms consist of uniform distributed isometric cells; however, such an assumption may be unsatisfied because organisms show fractal-like (hierarchical) organization, as pointed out by West et al. (1997). Furthermore, heterogeneous distributions such as log-normal distribution are widely observed in real-world systems (Limpert et al., 2001). Multiplicative effects and hierarchical organizations are known to generate log-normal distributions (Kobayashi et al., 2011). In particular, a simple model of fracture (Yamamoto and Yamazaki, 2013), originally proposed by A. N. Kolmogorov in 1941, is an instructive example, and it considers hierarchical divisions of one rod. Thus, we expected that such heterogeneous distributions of cell sizes resulting from the hierarchical organization lead to $B \propto M^{\gamma}$ with $\gamma < 1$ even if (mean) size of cell sizes is almost independent from body size.

Inspired by this fracture model, we propose a geometry model, called *fractal-like cube division (FCD) model* (Fig. 1). The FCD model can be interpreted as a 3-dimensional version of the fracture model; however, note that division processes are slightly different between the fracture model and FCD model because of the consideration

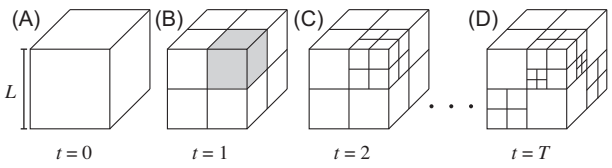

Fig. 1. Schematic diagram depicting the fractal-like cube division (FCD) model. (A) Cube with the length of L. (B) The cube of (A) is divided into eight cubes (cuboids) with the length of $L/2$. A cube (cuboid) selected at random (i.e., with the probability of 1/8) is indicated by gray. (C) As in (B), the selected cube (cuboid) is separated into 8 cubes (cuboids). (D) A state of the cube of (A) after T divisions.

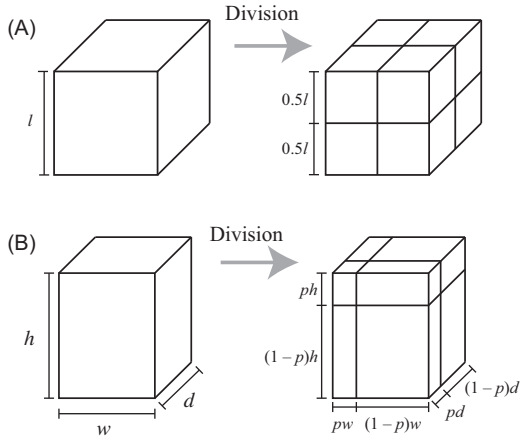

Fig. 2. Division rules of the simple FCD model (A) and general FCD model (B).

of fractal-like (hierarchical) organization of cell sizes (e.g., tree branches are more frequently divided than the tree trunk is).

We first explain a simple case of the FCD model. In the simple FCD model, the cube with the length of L (Fig. 1A) is divided according the following procedures. (i) The cube is divided into eight cubes (Figs. 1B and 2A). (ii) A randomly selected cube is further separated into eight cubes (Fig. 1C). (iii) The procedure (ii) is repeated until $t = T$ (Fig. 1D).

However, this division rule of the simple FCD model may be by the numbers. To consider more flexible divisions, we next propose a general FCD model. This model considers a division of the cuboid $C_{h,w,d}$ composed of the height of h, width of w, and depth of d, in the procedure (ii). In particular, this cuboid is divided into eight cuboids according to the parameter p drawn from a probability distribution with the range from 0 to 1 (e.g., uniform distribution $U(0, 1)$) (Fig. 2B): $C_{ph,pw,pd}$, $C_{ph,pw,(1-p)d}$, $C_{ph,(1-p)w,pd}$, $C_{ph,(1-p)w,(1-p)d}$, $C_{(1-p)h,pw,pd}$, $C_{(1-p)h,pw,(1-p)d}$, $C_{(1-p)h,(1-p)w,pd}$, and $C_{(1-p)h,(1-p)w,(1-p)d}$.

The general FCD model is equivalent to the simple FCD model when $p = 0.5$ at all times.

3. Results and discussion

3.1. Analytical solutions of geometric parameters

We here provide analytical solutions of geometric properties of the simple FCD model; however, the analytical results may be applicable to the general FCD model (see Section 3.2).

To obtain an analytical solution of the surface area of the simple FCD model using a mean field approximation, we consider the time evolution of the number $n_D(t)$ of cubes with the length of $(1/2)^D L$ when $D > 0$ (i.e., $t > 0$), where D denotes the cube division number.

$n_D(t)$ increases by 8 when a cube with the length of $(1/2)^{D-1} L$ is selected with the probability of $n_{D-1}(t)/N(t)$, and it decreases by