Biological Scaling Series

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Contents

1. Introduction

What does it mean to be alive? How would you define life? These questions are central to the study of *complexity and complex adaptive systems* (CAS). *Life* possibly represents the most complex phenomena in the universe and as such is difficult to define, let alone develop a unified set of theoretical principles for. Many branches of complexity science such as: reproducing cellular automata, genetic algorithms and random boolean networks, to name a few, explore aspects of biological life. Recent developments in genetic science has shed light on the dark matter of the human genome (previously thought of as 'junk' DNA) as actually containing millions of 'switches' which interact with the parts of DNA which encode genes. It seems our genetic material is orders of magnitude more complex than once thought — a true combinatorial explosion. The sheer complexity of biological life makes for scant principles or theories that can apply across the board to all biological phenomena. The *theory of evolution* is a notable exception. Another possible candidate is *biological scaling*.

Biological scaling or *allometry*, is the relationship between the sizes and/or rates of organisms. The correlation between body size and metabolic rate across a range of taxonomies is a major focus of allometry. The standard equation relating mass to metabolism is given in the following power law, where *power law*[1] simply means that variable *B* equals the variable *M* when *M* is raised to some power *a*.

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[1] [1] Power law relationships are often observed in nature as: self-organized criticality, i.e. earthquakes and avalanches. For more on power laws see the 'Zipfs Law and Power Laws" section.

$$B = Y_0M^a$$

where B is metabolism, Y_0 is a normalization constant, M is mass and a is the scaling exponent typically measured to be very close to 3/4.

Mass scales with metabolism to a 3/4 power law between organisms across much, if not all, of the biological domain.[2] First observed by Kleiber in the 1930's, the 3/4 power law applies to organisms across an incredible range of life processes, from the smallest unicellular organisms to shrews and hummingbirds to elephants and the largest living things (Fig. 1.1). "The life process covers more than 27 orders of magnitude in mass—from molecules of the genetic code and metabolic machinery to whales and sequoias..." (West, Brown 2004).
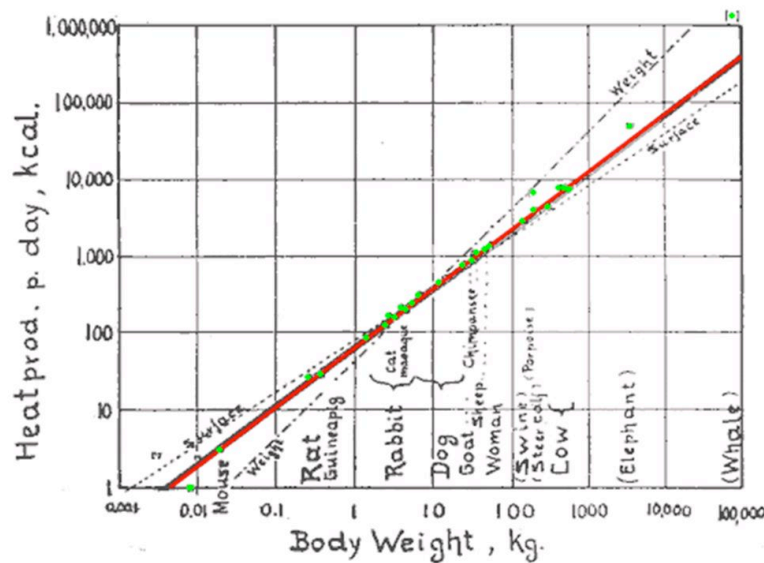

Fig. 1. Log. metabol. rate/log body weight

FIG. 1.1. Body size versus metabolic rate for a variety of species. Kleiber (1947). Kleiber's original units were weight and calories. Today units of mass and watts are typical.

Kleibers Law is interesting because it is unexpected. It was initially thought the relationship of an organism's size to its metabolism would be the same as volume to surface area or 2/3, the relation of the square of the radius of a sphere to the cube of the radius of a sphere. "Max Rubner reasoned that nature had figured out that in order to safely radiate the heat we generate, our metabolic rate should scale with body mass in the same way as surface area. Namely, he proposed that metabolic rate scales with body mass to the two-thirds power. This was called the 'surface hypothesis'..."(Mitchell 2009). Surface area was important in radiating heat and therefore related to metabolism. Because volume scales up much faster than surface area, it was as-

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[2] The 3/4 power law is one of many power laws in biology that have exponents in multiples of 1/4, called *1/4 power laws*.

sumed metabolism would slow down following a 2/3 power law to keep organisms from over-heating. Kleiber however, and many others since, have analyzed large quantities of data and determined the power law to be closer to 3/4 suggesting that larger organisms have a faster and hence more efficient metabolism than previously thought. Yet, until the mid 1990's, there was no theoretical basis to explain why[3]. Geoffrey West, Jim Brown and Brian Enquist have jointly studied Kleiber's law and have developed a theoretical model which describes the constraints underlying the phenomena. The West, Brown Enquist model (WBE), offers a comprehensive and inter-theoretic synthesis from multiple perspectives — West is a physicist, Brown and Enquist biologists — that elegantly describes the quarter power law behavior in terms of fractal distribution and uptake mechanisms. 'Brown and Enquist suspected that the answer lay somewhere in the structure of the systems in organisms that transport nutrients to cells. Blood constantly circulates in blood vessels, which form a branching network that carries nutrient chemicals to all cells in the body...Brown and Enquist believed that it is the universality of such branching structures in animals that give rise to the quarter-power laws' (Mitchell 2009).

WBE shows that metabolic efficiency increases (over that predicted by a 2/3 power) with higher level branching networks assuming the terminals of the network remain fixed or *invariant*. A vascular system, for instance, can distribute more resources to capillaries (terminal units) as the levels of a network increase than a volume to area model. In this sense, biological processes are more efficient the larger they become. Imagine for a moment the vascular systems of a shrew next to that of an elephant. Now imagine the elephant shrinking until it becomes the size of a shrew. There are many more capillaries in the elephant's system than in the shrew's. This means that the elephants metabolism scales up more than expected and partially explains why larger creatures: live longer, have longer gestation rates and sleep less than smaller ones. "An intriguing consequence of these "quarter-power" scaling laws is the emergence of invariant quantities, which physicists recognize as usually reflecting fundamental underlying constraints. For example, the mammalian life span increases as approximately $M^{3/4}$, whereas heart rate decreases as $M^{-1/4}$, so the number of heartbeats per lifetime is approximately invariant (about 1.5×10^9. independent of size" (West, Brown 2004). The WBE model defines a number of constraints or assumptions for a biological network. These are:

1. **The distribution network determines the scaling relationship**. "The relationship between metabolic rate and body mass is dominated by the structure and dynamics of the resource distribution network, which for most animals is the cardiovascular system" (Savage Deeds 2008).

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[3] The 3/4 power law is one of many quarter power laws observed in nature that are commonly referred to as quarter power scaling laws.

Metabolism[4] B equates with the volume of blood[5] *Vblood* in a given network. Mass M scales linearly with the number of terminal units (capillaries, leaves, etc.) in a given network.

2. **The distribution network is hierarchical.** "To say that the cardiovascular system is hierarchical amounts to assuming that there is a consistent scheme for labeling different levels of vasculature (Figure 1), proceeding from the heart (level 0) to the capillaries (level N). This assumption is not exactly true. For example, the number of levels from the heart to the capillaries in the coronary artery is smaller than the number of levels from the heart to the capillaries in the foot" (Savage Deed 2008).

3. **Vessels within the same level of the hierarchy are equivalent.** "All the vessels at the same level of the network hierarchy have the same radius, length, and flow rate. Again, this assumption is not strictly true but provides a tractable way to study an averaged network" (Savage Deed 2008).

4. **The branching ratio is constant.** At every level k the number of branches increases by the branching ratio n.

5. **The network is space filling.** WBE uses averaged networks which are cross sectional area preserving and space-filling, meaning they distribute to all service areas[6] in an organism.

6. **The energy loss of fluid flow through the network is minimized.** Network efficiency in terms of resources distribution and energy use has been selected for through the evolutionary processes of any particular organism.

7. **Capillary characteristics are the same across species.** The terminal units of all members of a given taxonomy are the same size, i.e. capillaries are invariant within a taxon. A related concept is that individual cells are the same size in different organisms.

8. **Capillaries are the only exchange surfaces and thus directly relate blood flow rate to oxygen supply in tissues.**

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[4] Metabolism here is generalized as the basal metabolic rate (MR) which is the MR of an organism at rest.

[5] Using overall blood volume as a measure for metabolic efficiency is problematic when applied to organisms without blood, namely unicellular organisms.

[6] A service area is the area around a given capillary that is given nutrients by the capillary.
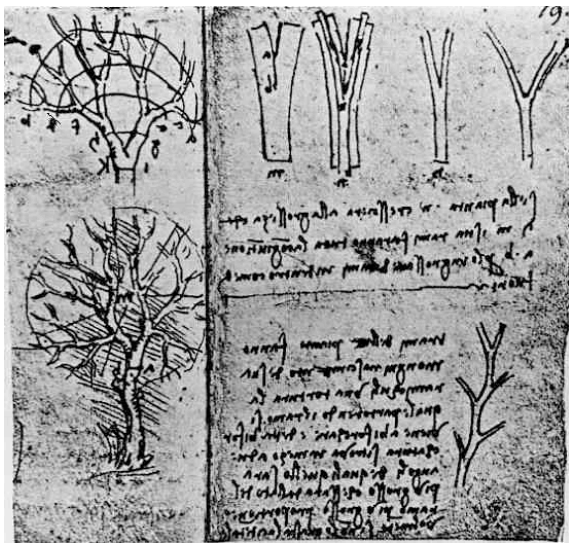
FIG. 1.3. Da Vinci sketch showing area preserving branches in a bifurcating fractal structure.

Assumption 5 above refers to the cross sectional area of a given branch of the network. The sum of all the cross sectional areas of the branches in a given level will be equal to the cross sectional area of the parent branch for that level. For instance, if a tree is made from many small pipes that each service one leaf, the trunk will be the collection of all the pipes, e.g. the sum of their areas. It is readily evident that this *pipe* model is independent of branch length. Area preserving branching networks were first recognized by Da Vinci ~500 years ago (see figure 1.3). The ratio of the radii of daughter branches to the radius of the parent branch is: $r_{k+1}/r_k = n^{-1/2}$ where n is the branching ratio (2 for bifurcating) and k is a given level. This ratio is referred to as β (see Fig 1.4). In the related Netlogo models for this writeup this equation is re-written as: $r_{k+1} = r_k / n^{1/2}$.
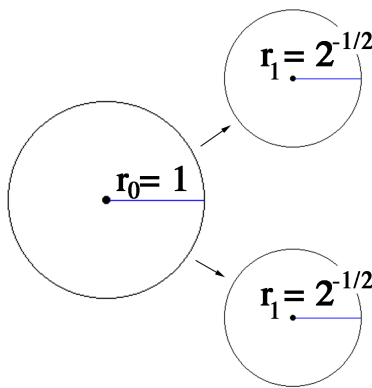

FIG. 1.4. Area preserving relationship for bifurcating structure, (n = 2).

Assumption 5 also refers to the service-volume of a characteristic length of the network ℓ^3. The sum of the volumes for the characteristic lengths in a given level will be equal to the characteristic volume for the parent branch. The ratio for the sum of volumes for daughter branches to the volume for the parent branch is $\ell_{k+1}/\ell_k = n^{-1/3}$. Where n is the branching ratio and k is a given level. This ratio is referred to as λ. It is perhaps more clear to visualize a cube splitting into two cubes which together equal the volume of the initial cube (see Fig 1.5). In the related Netlogo models for this writeup, this equation is re-written as: $\ell_{k+1} = \ell_k / n^{1/3}$.
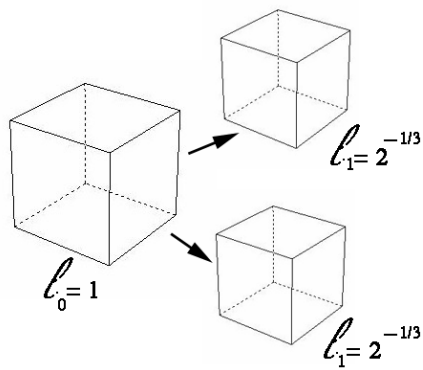
FIG. 1.5. Volume preserving relationship for bifurcating structure (n = 2) with characteristic length of the network ℓ.

The basic WBE model is simply the log (any log, i.e. natural log etc.) of the total number of capillaries N in a given network over the log of the product of λ and β^2 (see *appendix* for a more detailed derivation of the WBE model).

$$a = - \ln N / \ln \lambda(\beta^2)$$

Solving for *a* we get

$$a = - \ln N / \ln N^{-1/3} * (N^{-1/2})^2$$
$$a = - \ln N / - 4/3 \ln N$$
$$a = 3/4 \ln N / \ln N$$
$$a = 3/4$$

The WBE model uses an averaged fractal branching structure where an initial branch in a given network such as an aorta or trunk splits into successively smaller branches scaled to the ratios λ and β and terminating at a capillary or leaf. This structure is self similar and recursive for a given number of branching levels k. The diagram below (Fig 1.6) shows a network of 3 levels with a branching ratio of 2.
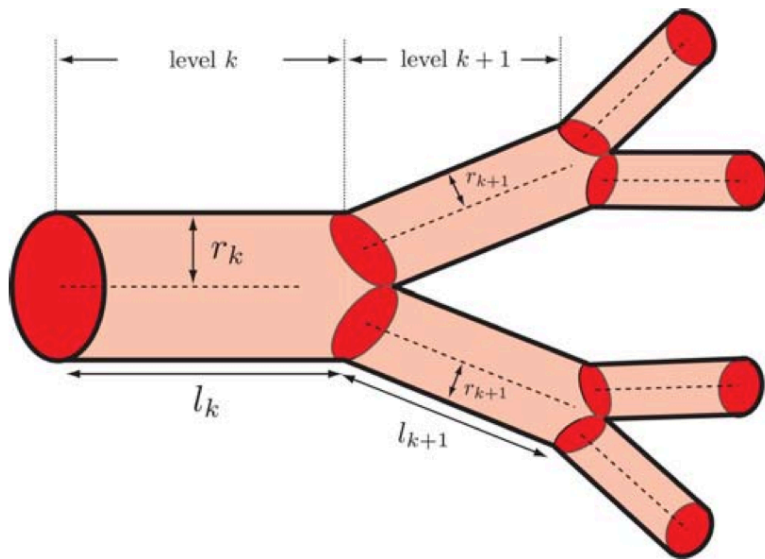
FIG. 1.6. Hierarchical branching structure in an averaged network. Level K branches into two daughter vessels at level k + 1. The branching ratio = n = 2. r_k = radius and l_k = length of branch (Savage Deeds 2008).

The WBE model has been applied to many areas of biology and is generally called metabolic scaling theory or simply metabolic theory. Like many inter-theoretic theories, metabolic theory is elegant in its simplicity. By positing *fractals* as the prime constraints in biology, life — in all its variety and complexity — has a universal organizing principle which may be rigorously explored with the tools of science. In the words of West, Brown and Enquist, "We see the prospects for the emergence of a general theory of metabolism that will play a role in biology similar to the theory of genetics" (West, Brown Enquist 2005).

2. Biological Scaling with Fractal Geometry

Quick Overview

Biological scaling with fractal geometry (simple-bio-scaling.nlogo) is a model that illustrates how Kleiber's law is represented by biological fractal networks viz. the WBE model. Prerequisites for this section are a firm foundation in basic algebra, trigonometry, logarithms and summing a geometric series. Fractals networks are clearly visualized 3 dimensionally with multiple levels and branching patterns. A scatter plot and linear regression show the power law of 3/4 associated with Klieber's law using the WBE model as well as other models. Fractal geometry applied to biological phenomena offers a unique way of understanding the complexity of biological forms and their functions.

Learning Targets

1. To familiarize an undergraduate or graduate student with basic principles relating to allometric biological scaling and complexity theory. Students should have a basic understanding of rules of exponents and logarithms.

2. To familiarize an undergraduate or graduate student with Klieber's law and the West, Brown, Enquist model which derives the well known 3/4 power law between body mass and metabolism.

3. To illustrate the WBE model in a visual format that explains the assumptions of the model in tangible geometric terms. In short, a visualization of: $3/4 = - \ln N / \ln \lambda(\beta^2)$

Background

Scaling relationships in nature do not simply increase or decrease in size isometrically, e.g. a distance preserving mapping, but rather *allometrically* which is to say they vary depending on how large or small an organism is. The femur bone of a mammal, for instance, increases in cross section in 2 dimensions as the body size increases in 3 dimensions, meaning that it must now support 3X the weight but is only 2X as large. Consequently, a mastodon's femur is proportioned differently than a mouses' and is thicker in cross section than a mouses' would be if the mouse were scaled up to be the same size as a mastodon (see Fig 2.1).

FIG. 2.1. Femur bone of a mastodon (top) compared to that of a mouse (bottom).

Allometry is the study of how the shape and proportions of an organism change with size throughout its ontogeny and in comparison to other organisms. Kleiber's law, shows a linear relationship across many different classes of organisms between body mass and basal metabolism. By 'linear' it is meant that data scatter plotted on a log-log graph with body mass on the x-axis and metabolism on the y-axis will reveal a straight line with a slope of 3/4 after a linear regression is performed. This correlation across much of the organic world is striking and the subject of heated current debate (Agutter, Wheatley 2004). West, Brown and Enquist (WBE) have developed a theory that explains this linear correlation by introducing the inherent efficiency of fractal geometry in nature. Fractal geometry can be observed in all creatures great and small, according to this theory, and is the basis for allometric scaling relationships in everything from unicellular organisms to great blue whales and even entire forests. The gist of the idea is that fractals found in nature have properties, less friction and impedance for instance, and because of this inherent utility have been selected for over the eons

by evolutionary processes. This idea certainly makes sense when observing distributive networks involving fluids such as vasculature. It is a little more obscure when applied to microscopic organisms that do not have obvious fractaline distributive networks in their systems. For this reason, the models in this series focus on vasculature fractal networks where the main branch is analogous to the trunk of a tree or the the aorta in a mammalian arterial system and the subsequent branches are literally *branches* or arteries ending in leaves or capillaries. As previously mentioned, leaves and capillaries are considered scale invariant terminal units across a given taxon. For instance, the capillaries of an elephant and a mouse are the same size. An explanation for this is that chemicals in the blood, e.g. hemoglobin and oxygen represent a constraint that fixes the size of arterioles. The network, in a sense, builds backwards from there. Organisms of different sizes have different numbers of levels in their networks but otherwise are the same. Also, the WBE model assumes these fractal networks are cross-sectional area preserving and space filling with branching ratio or 2, i.e. a bifurcating fractal structure (see section 1). With these basic constraints it is possible to build a model which demonstrates Kleibers law in terms of fractal geometry alone. This has caused quite a stir in biology as well as physics and has not been without controversy as will be discussed more in the conclusion to this series. However, regardless of criticism of the WBE model, it is significant in being the first macro-biological theory to link fractal distribution networks with metabolic scaling theory.

Netlogo Model Interface

Please open the model, *simple-bio-scaling.nlogo*. In the upper left hand corner of the interface, press the buttons in this sequence *Clearall —> Setup —> Go*. A fractal network should begin building in the 3D view of the interface. Explore the various buttons, sliders and switches to get a general idea of how the model works.

The network is made form cylinders or *vessels* colored white which begin at a certain diameter and length controlled in the interface and branch into successively smaller and smaller tubes until the terminal size of .1 is reached, at which point a capillary is sprouted consisting of a red sphere with arbitrary dimension. An initial diameter is set by the *init-dia* slider which controls the diameter of the first tube. The init-dia slider is located just below the 'go' button (Fig2.2). Remember that one of the assumptions of the model is that the terminal units (capillaries) are the same size over any number of levels k, so in a sense then, the sizes of vessels are determined backwards. *Size* in this model is considered the *diameter* of the tube. Because the area preserving relationship is a simple ratio: $\beta = n^{-1/2}$, it applies equally as well to diameter as it does to radius. The slider *init-dia* sets the initial diameter for any given level based on successive scalings of the terminus to the ratio β. The terminus is sized to be .1000, therefore, initial tube diameters for successively higher levels are .1000, .1414, .2000, .2828 etc.

The *init-length* slider controls the initial length of the first vessel of the network also referred to as the *trunk*. Length is a ratio based on service-volume preserving attributes for the entire network. This does not refer to the volume of the tubes but rather to a volume of a space around the vessels which can be thought of as a *service volume*.
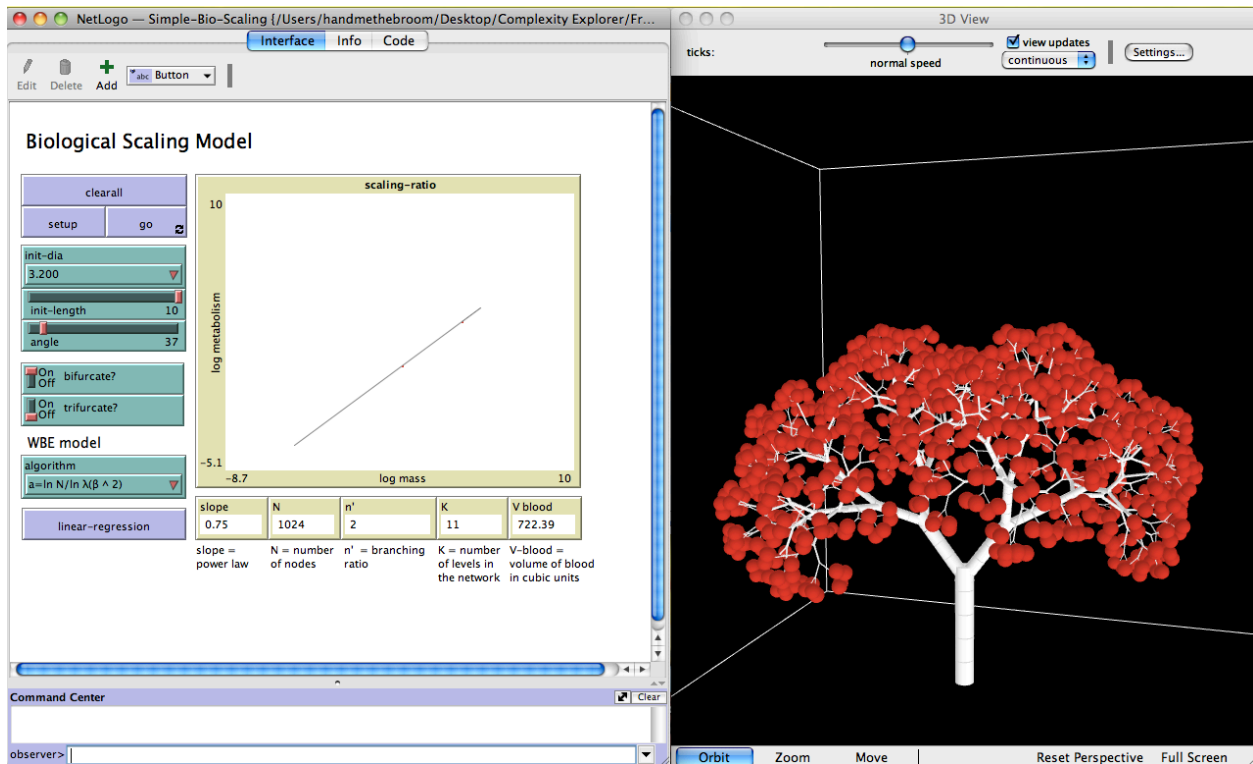

FIG. 2.2 Biological scaling model with fractal networks of different levels k with a linear regression of .75.

CODE: Click on the *Code* tab in the upper part of the screen and take a look at the various procedures used in the program. The procedures are named, aptly enough, after the process of growing a tree. After pressing setup, the *make-tree* button initiates the following series of procedures: *seed —> trunk—> branch—> bud*. The structure cascades into ever smaller branches until they reach the invariant terminal size, at which point *buds* are formed and the program stops. The system is also analogous to a circulatory system, i.e. *aorta, arteries/vessels, capillaries*, and this terminology is found in the literature as well. After building a tree a data point will be added to the plot labeled *scaling ratio*. This point is determined by the metabolism B to mass M ratio[7] as given by the WBE model.

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[7] The actual mathematical definition for B/M is fairly complicated and discussed more in the index section of this series.

Try building a few more trees with different initial diameters to plot some more points in the graph. To do this you need to first choose a new diameter in the chooser *init-dia* and then press *setup* to erase the old tree and seed for the new diameter and then *maketree*. Do not press *clearall* or else you will clear all the data points from the graph. After plotting a few more points, try pressing *linear-regression* to plot a best fit line for your scatter plot[8]. As you hopefully see, the points lie on a straight line with a slope of 3/4. This is the 3/4 power law we are familiar with.

THINGS TO NOTICE: It is possible to build a tree with a branching ratio of three instead of two by turning off the switch *bifurcate* and turning on *trifurcate*. You may notice that the linear regression has the same slope = 3/4. How could this be possible? A different structure should have a different overall volume and node count. If you look at the values for the variables nodes *N* and volume of blood *V-blood* you may see that indeed these values *are* different for different structures with the same number of levels *k*. The reason for this discrepancy is that the WBE model has basic assumptions built into it, one of which is that the network has a branching ratio of 2. When we switched the ratio to 3 we did not change the assumptions built into the model (this could be done but it would involve a lot of math) and therefore the power law is still 3/4. It is important to realize that the WBE model is a generic one using an averaged network with very tight constraints. Try switching off *trifurcate* and turn on *bifurcate* once again and make a tree. This is the averaged network WBE is based on and the main pedagogical objective of this netlogo model. It turns out that all you need to know to determine the 3/4 power law for the WBE model is the number of nodes in the network! This is true because the network is built into the mathematics. Try subbing in some values for N into the equation :

$$a = - \ln N / \ln \lambda(\beta^2)$$

$$a = - \ln N / \ln N^{-1/3}(N^{-1/2})^2$$

$$a = - 1 * \ln N / \ln N^{-1/3}(N^{-1})$$

$$a = - 1 * \ln N / \ln N^{-4/3}$$

$$a = - 1 * -3/4 (\ln N / \ln N)$$

$$a = - 1 * -3/4 (1) \text{ for } 1 < N < \infty$$

$$a = 3/4$$

This may feel somewhat anticlimactic but bear in mind the actual model goes into much more detail involving the fluid dynamics of organic networks and impedance at branching intercepts. Van Savage et. al. in *Sizing Up Allometric Scaling Theory* analyzes the model in some of its

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[8] The linear regression uses the sum of least squares to determine the straight line that fits the data (shortest distance between each point and the line along the y-axis).

more complex dimensions including a more detailed discussion of the models assumptions.[9] The value of the model may be deceptively simple. It rests on the distillation of the myriad of life's complex networks into an 'averaged' network that identifies the salient aspects of these biological systems, namely their utility function. The netlogo simulations presented here and in the next section allow for the generalized model to be taken back into the field so to speak and explored as heterogenous structures with the capacity to evolve towards an optimal state based on the WBE utility function. The utility function is the maximum of the number of terminal nodes or capillaries B (metabolism) per minimum network volume M (mass).

FOURTH DIMENSIONAL FRACTALS: It is possible to derive the 3/4 power law from the simple ratio of length cubed over length to the fourth power: $a = \ell^3 / \ell^4$. A log-log plot of this relationship will be a straight line with the familiar slope of 3/4. The relationship between the third and fourth powers has led West and others to posit that biology has evolved fourth dimensional networks. These networks operate in three dimensions but have somehow harnessed another degree of freedom within these spatial constraints. West et. al. write:

"Unlike the genetic code, which has evolved only once in the history of life, fractal-like distribution networks that confer an additional effective fourth dimension have originated many times. Examples include extensive surface areas of leaves, gills, lungs, guts, kidneys, chloroplasts, and mitochondria, the whole-organism branching architectures of trees, sponges, hydrozoans, and crinoids, and the treelike networks of diverse respiratory and circulatory systems. It is not surprising, therefore, that even unicellular organisms exhibit quarter-power scaling, including the 3/4-power scaling law for metabolic rate. Although living things occupy a three-dimensional space, their internal physiology and anatomy operate as if they were four-dimensional." (West et al 1999).

Exercises

1. The WBE model uses a simple mathematical algorithm to determine the 3/4 power law relation between mass and metabolism. The WBE model is labeled 'a=ln N/ln λ(β ^ 2)' in the scroll down chooser labeled *algorithm*. This model is programmed in NetLogo with the following code:

```
if algorithm = "a=ln N/ln λ(β ^ 2)"

[let λ N ^ (-1 / 3)
let β N ^ (-1 / 2)
set metabolism   log( N )10
```

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[9] For instance, Savage points out that for small vessel sizes and organisms with a low number of levels, i.e. small organisms, there can actually be area *increasing* branching. This is important because the blood is not at a constant velocity through a circulatory system but must slow down at the capillaries so the blood has time to diffuse into the surrounding service volumes. As technologies in imaging advance and become available to researchers ,more precise measurements of organism networks will be done and undoubtedly elucidate the WBE and other models.

```
set mass -1 * log(( λ * (β ^ 2)))10]
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The mass of the network M, is defined by the number of branches n and levels k in the network which determine the overall volume of blood in the network which is assumed to scale linearly with body mass. Metabolism is simply the number of terminal nodes in the network.

M — mass (linearly proportional to volume of blood)
B — metabolism (number of terminal units)

The equation $a = \ln N / \ln \lambda(\beta^2)$ yields $a = 3/4$ for any number of terminal nodes $N > 1$. This is because the model represents an 'average' network which makes certain simplifying assumptions , for instance, the angle between vessels is not included in the model. The main assumptions are: that the network is bifurcating and all the vessels at any given level k are the same (see the appendix for a detailed derivation of the above equation). Suffice it to say, the model is fairly generic. Can you devise a different model that also yields the 3/4 exponent. For the apt reader, perhaps this involves other branching ratios and vessel lengths/sizes. Coming up with an actual model is not as important as outlining the parameters and variables you would include in your model.

2. What do you treat endogenously? What is excluded? How might your model be verified in a biological organism?

3. A few other examples taken from the literature and of the authors own invention are given in the chooser *algorithm*. Can you implement your model in the Netlogo code and add it to the chooser?

3. Biological Scaling with Genetic Algorithms

Quick Overview

Biological scaling with fractal geometry using genetic algorithms (*intermediate-bio-scaling-GA.nlogo*) is a model that illustrates how 3/4 power law scaling in biology (Kleiber's law) is represented by biological fractal networks which evolve by means of genetic algorithms. Prerequisites for this section is the *Genetic Algorithm series* as well as a firm foundation in basic algebra, trigonometry, logarithms and summing a geometric series. Fractal networks are randomly generated and selected for based on a utility function. The utility function is the maximum of the number of terminal nodes or capillaries B (metabolism) per minimum network volume M (mass). Fitness = max B/M. Multiple networks are possible to evolve

which satisfy the WBE model. Network fractality is examined as a basis for biological scaling in nature.

Learning Targets

1. To familiarize an undergraduate or graduate student with allometric simulations using genetic algorithms.

2. To apply genetic algorithms to biological scaling models. Concepts such as fitness function/ utility function, cross-over, tournament selection, and mutation are explored within the context of biological fractal distribution networks.

Background

The WBE model posits that biological fractal networks such as vascular networks, circulation networks, veinous networks etc. are space-filling fractal structures selected for over millennia based on efficiency. Space filling networks offer utility to an organism by allowing the efficient distribution and uptake of resources to an entire organism's body mass. For instance, the pulmonary system, with a fractal dimension approaching 3 (space filling) is highly specialized to allow for the maximum surface area to deliver oxygen to the blood [10], hence the proverbial, 'if the surface area of the lungs were spread out flat it would cover a tennis court'[11]. The size of the red blood cells (hemoglobin/oxygen solution) in turn determines the capillary terminus for the network. Maximizing the number of terminals is another space filling characteristic of the circulatory system. Terminals are scale invariant across many life forms based on universal constraints such as cell size. The WBE model assumes a space filling network based on scale invariant terminals and posits that larger organisms have more efficient metabolisms than expected because there are more levels k in their fractal space-filling networks. Larger branches have less resistance, so a structure that maximizes the number of large branches and minimizes the number of short ones is inherently more efficient.

A related example in transportation infrastructure demonstrates the efficiency of larger cities. Imagine transportation infrastructure as a fractal space filling network. Larger cities employ the economy of scale with vehicular distribution networks consisting of hi-ways, boulevards and

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[10] The pulmonary system has a fractal dimension of 2.97, close to 3, making it nearly space filling and the surface of the brain is also fractal in composition, with a fractal dimension of 2.79 (Wikipedia).

[11] It's commonly said that if you were able to extract all 300 million (or so) of the lungs' alveoli (the smallest units of gas exchange), unravel each so it formed a flat piece of tissue, then lay each alveolus down side by side, they would cover an entire tennis court. Has this ever been done? Heck no. But approximations have been made, and it seems like this is relatively correct (Wikipedia).

street grids etc. Hi-ways are bifurcating fractal structures — no wonder they're called 'arteries' — with relatively low viscosity (traffic, traffic lights) compared to a neighborhood scale street grid. Hi-ways are like the trunks of trees branching in ever decreasing size to neighborhood street grids which allow for redundancy in their networks; whereas, hi-ways do not, i.e. there is only one way to get from point *A* to point *B*. This is reflected in the looped arteries within the terminal node of a tree — the leaf. An explanation for this is that leaves are subject to damage — tears, insect invasion etc. — and therefore incorporate redundancy making them more resilient. Organs like the heart and brain are also more redundant networks for perhaps similar reasons — resiliency to heart attacks and strokes.
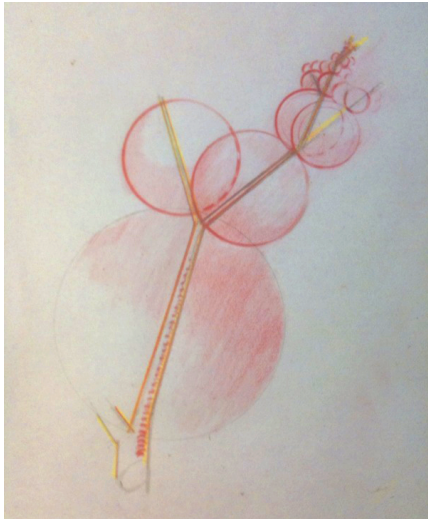

FIG. 3.1. Space filling fractal network showing both area preserving and volume preserving characteristics..

It may be difficult to wrap your head around the idea that biological networks could be area preserving *and* volume preserving simultaneously. The key is to realize that the *area preserving* part refers to the cross sectional area of the individual vessels always equalling the sum areas of their daughters. *Volume preserving* refers to the service volume of the capillary which is assumed to be scaled linearly across all the levels. A simple diagram (Fig 3.1), offers a visualization of service volumes scaling through the levels of a network. Imagine spheres with diameters equal to the lengths of branches who's volume is equal to the sum of the volumes of the daughter branches. This is the sense of *volume preserving* in WBE which is used synonymously with *space filling*. It is important not to confuse this service volume with the *vessel's volume* which plays an important role in the WBE model. The vessels volume, by the way, is simply the volume of a cylinder whose area is the cross sectional area of the branch times its length. The WBE model is vessel volumes reducing as the lengths of vessels reduce as they progress from trunk to terminus. Vessel volume preserving coupled with cross sectional area preserving would require daughter branches to be the same length as parent branches for a bifurcating tree.[12]

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[12] A bifurcating network that is cross sectional area preserving *and* vessel volume preserving has daughter branches equal to the lengths of the parent. Say the radius and length of the parent cylinder are both 1, the volume is *area * length* so the volume is 3.14. The radii of the daughters would be .707 (Beta = -1/2) and their areas = 1.57 so the daughter's lengths would have to be 1 to have their combined volumes = 3.14.

A network such as this is analogous to arteries and service volumes in a circulatory system[13]. All the organism must be provided for, so the sum of the service-volumes equals the total volume of the organism, and given the density, which is assumed to be constant across individuals and species, it is straightforward to convert this into body mass. Service volumes in actuality are packed together so may look more like polyhedra — imagine soap bubbles packing. The number of capillaries in an organism is assumed to be proportional to metabolism. Once again bear in mind, WBE posits an averaged network which applies across the board to virtually all of life and by necessity is highly abstract and serves more as a basis for assumptions in the model than a strict description of how networks are specifically structured or space filling volumes physically pack in an organism. Indeed there are many different types of fractal structures that have evolved in biology. The next model in the series, *intermediate-bio-scaling-ga.nlogo3d*, investigates space filling characteristics further using *genetic algorithms*.

Netlogo Model Interface
Biological Scaling with Genetic Algorithms

Please open the model, *intermediate-bio-scaling-ga.nlogo3d*. In the upper left hand corner of the interface, press the buttons in this sequence *Clearall —> Setup —>*defaults*—> multiple runs*. A series of dynamic networks should begin building in the 3D view of the interface. Explore the various buttons, sliders and switches to get a general idea of how the model works. The network is designed to have a maximum of 3 levels. The defaults should produce a model similar to the one below (Fig.3.1). The three levels have distinct lengths that scale non-linearly. Do a number of runs and observe the lengths change in the upper left plot labeled *Length of Branches*. The level 1 branch length is usually, but not always, longer than the level 2 branch length. Sensitivity to initial conditions is evident early on as lengths quickly become locked in to a fractal-like hierarchy. The trunk is typically the shortest branch as its length does not affect the space filling characteristics of the network. Indeed, if the mutation rate and strength is turned up the trunk may decrease to zero.

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[13] Another useful analogy is the ductwork in a building's HVAC system. Imagine two heating registers at the ends of daughter ducts which combine to form a larger branch. The combined volume of the space heated by each register is equal to the volume of the space that could be heated by the parent duct.
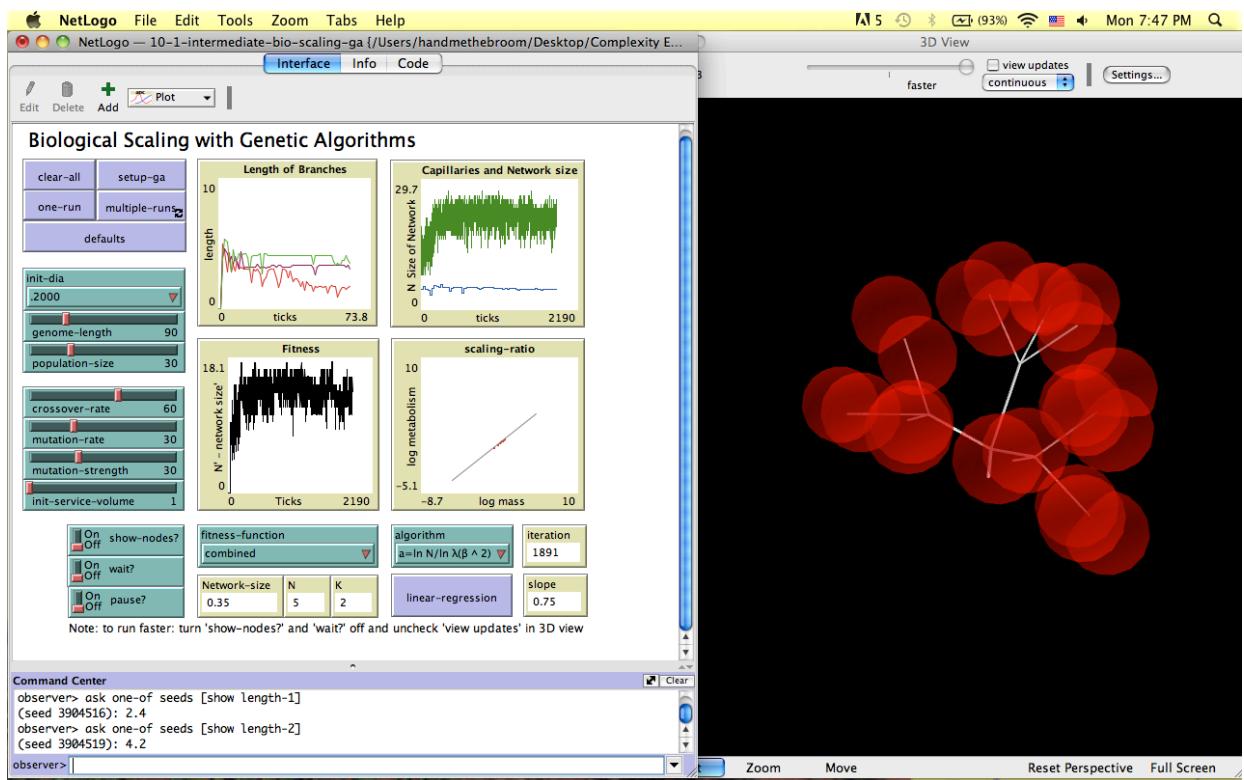
FIG. 3.1 Evolving biological network simulation..

This model is designed to select t he networks from an initial population with the highest utility functions. The utility function is simply the maximum number of terminal nodes, called nodes N, to the minimum volume of the network, termed *network-size*. For this model, the *network size* is considered the sum of the volumes of the vessels, (cross sectional area times the length of the branch). This should not be confused with the *volume of blood* in WBE which refers to the service volumes of the network (see appendix).

Before getting into the specifics of how genetic algorithms are used in this model, it is helpful to get an intuitive understanding of the model by modifying the default settings and doing a few runs. You may notice in the plot *Length of Branches* that the lengths of the vessels get smaller over time. In the plot labeled *Nodes and Volume of Blood*, the node count increases as the volume decreases. This corresponds to the increased fitness of the model over time shown in the plot *Fitness*.

Now that you have a basic feel for how the model is setup try exploring the procedure *create-next-generation*. A genetic algorithm is a way of practically selecting desirable outcomes over a large search space. The method for doing this replicates the process of natural selection. As such, the primary elements of a GA are *inheritance, mutation, selection and crossover*. The particular GA used here is called tournament selection, where the best fitness solution is chosen from a population by choosing the best fitness from a random selection of three with replacement. This

is repeated until a new generation is formed and the old generation is dismissed. Heritable traits in this model are binary strings of length determined by the slider *genome-length*. These strings are referred to as DNA in the model and define the length of the vessels as well as the angles of branches and the branching ratio. These *heritable* variables are modified through crossover, cloning and/or mutation and passed along from one generation to the next. Crossover involves two parents combining their DNA with a random split point and swapping of the subsequent substrings. Cloning is simply taking the best fit from one sample and giving it to the offspring. All of the old population who are not 'mated' in the crossover procedure are cloned. Mutation is a random modification of the DNA strings, replacing a varying number of randomly selected bits with either a one or zero. Mutation in this model has two settings: a *mutation-rate* and *mutation strength*. Mutation rate is simply the number of the new population (both crossovers and clones) who are subjected to mutation. Mutation-strength is the number of times the process of randomly changing bits occurs, a higher mutation strength randomly alters the string more. The reporter procedure below is choosing a random item from the overall string length and replacing it in the string with a binary, either a one or zero.

```
to-report mutate [string bits]
[report replace-item random length string string bits
]
end
```

Now that you are somewhat familiar with the basics of the model, try increasing the init-dia slider to .4000 and run the model with the defaults or with your own modifications to the parameters. To speed up the model, turn the show-nodes? and wait? switches off at the bottom left hand corner of the interface (Fig 3.2) and uncheck the view updates box in the 3D view (Fig 3.3). The model is composed in three parts separated in the code as *make seeds, make tree and make next generation*. These categories of procedures are basically: defining a seed population with genetic information (the DNA strings), growing the seeds into trees with certain attribute (size and number of nodes) and selecting for those with the best fitness (nodes - size) to create a new generation of seeds and begin the process again. Each seed has genetic material defined as bit strings which set variables such as branch lengths and branch angles. A range of seeds, trees and selection processes can be controlled with built in parameters in the model. The following is a list of each control on the left-hand portion of the interface and a brief description of what they do.

Init. Dia: Sets the initial diameter of the first branch which is referred to as the *trunk* in the model.

Genome-length: Defines the length of the bit string for each seed variable. The ones and zeros in each string are added together to set the value for a particular variable. For instance say the string [001101] is the length-0 variable. This means the first branch (trunk) will be 3 increments long.

Population-size: Defines the number of seeds used in the model. This number never changes as the old generation makes exactly the same number of offspring and then dies with no overlap.

Crossover-rate: This is the percentage of the number of individuals in the old population used for crossover (mating) to create the new generation. The percentage of the population remaining are cloned.

Mutation-rate: This is the percentage of the population which mutate.

Mutation-strength: Defines the number of times a string is subjected to mutation.

Service-volume: Defines the number of nodes at any given terminus. Terminals are the ends of the last level of branches which consist of capillaries and nodes[14]

FITNESS FUNCTION: The way the genetic algorithm selects genes to propagate is by choosing seeds with the highest fitness function (FF) which is a simple scaler value. There are multiple FF for that can be selected. Go to the code section of the model and scroll down the procedures tab to *calculate-fitness*. It should look like this:

```
to calculate-fitness
   if fitness-function  = "service volume - network size" [
  ask seeds [
set fitness  service-volume - (network-size') ]
   ]

   if fitness-function  = "service volume - capillaries" [
  ask seeds [
set fitness  service-volume - N ]
   ]
end
```
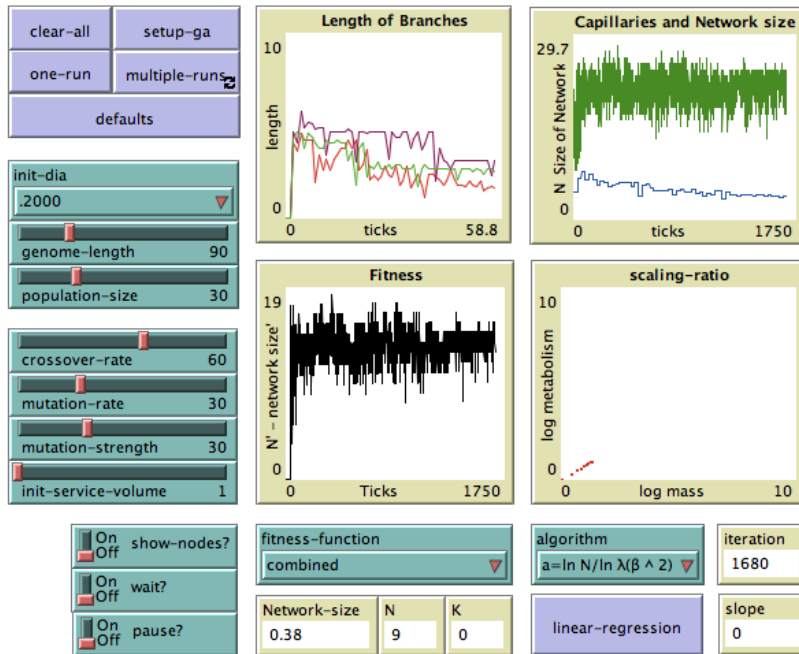
The simulation is designed to select for the maximum number of nodes and the minimum network size or number of capillaries. Higher node counts with smaller networks will have the highest FF. Networks can evolve to have bifurcating or trifurcating branching structures. Branching structures together with the setting for service-volume creates an initial number of nodes around a given capillary *but* nodes die if they overlap, so the branching angle and lengths of branches also come into play to define FF. The variable service-volume refers to the number of nodes. The variable network-size refers to the sum of the volumes of the vessels in the network. The variable capillaries refers to the number of terminals which is the same as the number of

---

[14] Each terminal has only one capillary but several nodes which define the service volume for the network. Nodes are analogous to biological cells receiving nourishment and distributing waste into the arterial and veinous networks supporting them.

branches at the last level, i.e. the network depicted in figure 1.6 would have 4 capillaries. All of these variables are different for different seeds so the FF values are unique and thereby selectable.

FIG. 3.2 Model interface at about 60 ticks.

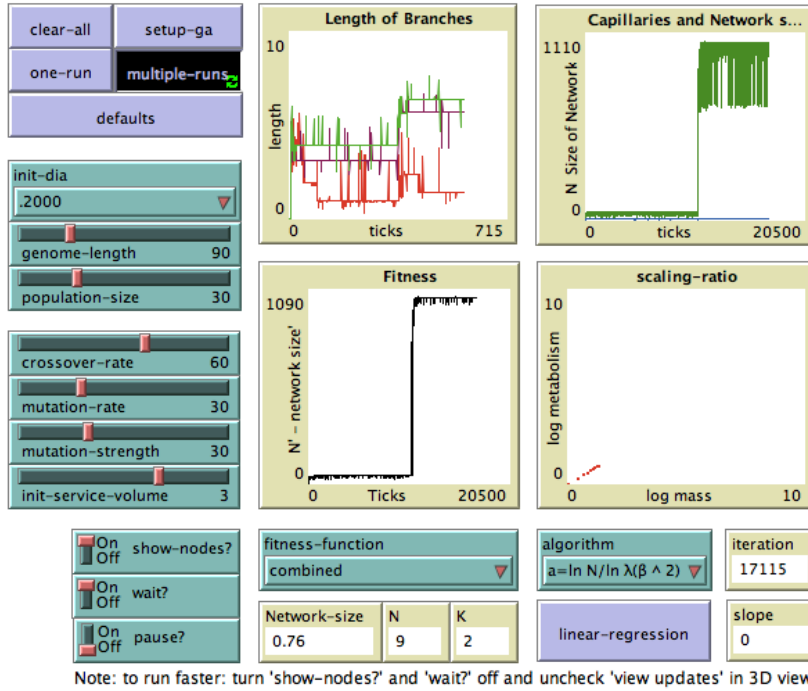## Biological Scaling with Genetic Algorithms

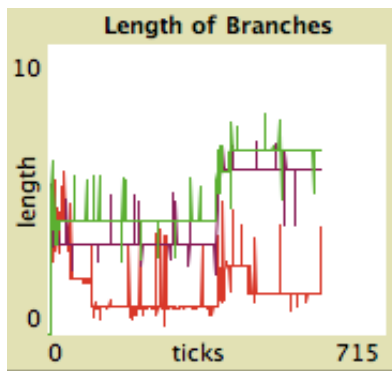**FIG. 3.3** Model interface at 290 ticks.

FIG. 3.4 Lengths of branches at 3 levels with different sized service volumes.

The screen shots above (Fig 3.2, 3.3, 3.4) show the progression of branch lengths over a couple of intervals. A distinct tripartite division is clear and dependent on service volume size. Branches settle on a local optimum temporarily but may suddenly shift as mutant variations become available and are selected for. This simulation attempts to evolve a fractal network based on a few simple assumptions and rules. The degree to which it is successful is multi-faceted. The trunk consistently shrinks which is expected as it doesn't change the space filling characteristics of the overall structure. Intermediary branches oscillate relative to one another, meaning that if one decreases in size another increases and vice versa.

THINGS TO NOTICE: Try sliding the mutation rate down to zero and the crossover rate to around 50 and do a few runs. Notice that the population does evolve for a while with only cross over and cloning at play but eventually reaches a local maximum and flatlines. Mutation *must* be introduced to create variety in the genome and a chance for new forms to evolve. Using only a two level network is a simple way to see this interaction at work. The smallest volume network has the shortest branches yet the limit as branch length approaches zero is asymptotic, this is because the probability of mutating the necessary bits (a one to a zero) becomes less and less as there are fewer and fewer ones to randomly select. After all, the overall state space is a power law itself, equal to bits$^{\text{string-length}}$, 2^x. A string of length 30, for instance, has a state space of over a billion. As the string length increases, the state space grows exponentially. So, as our branch length becomes smaller it gets increasingly improbable that it will become smaller yet.

EXTENDING THE MODEL: An interesting extension of the model, given in the *exercises* section, is to allow the mutation-strength to vary over time and be an additional variable selected for. When mutation decreases over time a system is said to simulate the process of *annealing* an analogy to metallurgy where the temperature of a metal changes its properties and by careful management of heating and cooling, properties can manifest in metals such as softness or hardness etc. Mutation-strength can be thought of as temperature and varying this variable, a simulation of annealing. However, this model only allows for fixed values of mutation strength. An extension of the model would be to add variable constraints for mutation strength. These constraints could be environmental ones which affect the genome, i.e. temperature.

Relevance to WBE: The second fitness function in the simulation is most like WBE in that the service volume represents the total volume of blood which translates to mass *M* and the capillaries represent metabolism *B*. However, the service volumes in this simulation are created at the final level of the network. In WBE, the service volumes scale with each branching level and are space filling. The WBE network may be thought of as *service volume preserving* in addition to area preserving. The simulation also uses trifurcating structures which are not in the WBE model which posits that there is more impedance at trifurcations, slowing down blood flow and not selected for in biological evolution.

Exercises

1. Design a default setting that has better fitness than the existing defaults. It may be helpful to use behavior space and test a number of different settings for crossover-rate, mutation-rate and mutation-strength.

2. Extend the model by allowing for mutation strength to vary over time. Simulated annealing is associated with temperature. A temperature control could increase mutation strength with temperature and allow it to gradually cool, giving the model more sensitivity when it is most needed. Larger mutations may help the model evolve quickly but smaller mutations are necessary later on to *fine tune* the model.

3. What phenotypic types might increase fitness? Introducing more stochastic processes into the *make-tree* procedure introduces heterogeneity in the models. Try extending the model to allow for environmental influence to interact with the growth process of the network.

Just for fun

4 a. Trifurcated structures tend to evolve in this model because they have $k^{\text{branching structure}}$ more capillaries than a bifurcated structure. This is not observed in biological systems so much. Try creating a weighted cost for trifurcating structures using a slider in the interface. Is it possible to eliminate the trifurcating structures?

b. Seeds have the same branching ratios for all levels (and angles by the way). If you are feeling adventurous, create the possibility for different branching ratios and angles to occur at different levels (you will need to make a new DNA string for each added parameter). Is it possible to evolve a network with trifurcating branches on some levels and bifurcating branches on others by adjusting your weight gradient?

c. Invent your own variables to add to seeds' selectable traits. These could be additional DNA strings or environmental factors.

CRITICISMS OF WBE: In WBE, abstractions of real networks, such as vascular networks in human beings, are necessarily generalized to apply to many examples where definitions may become more ambiguous or serve as analogies rather than strict isomorphisms between the mathematical model and real world networks. For instance, in a service volume preserving network such as WBE, it is not clear what constitutes the service volume being preserved (or network for that matter) for microbial organisms. Further ambiguity is introduced in referring to spatial networks as *fourth* dimensional, what exactly constitutes the fourth dimension here?[15]. Analogy and description gets a little blurry in WBE and has fed criticism. For a good outline of the major

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[15] Blum derives the 3/4 power law in 1977 based on a hyper sphere in the paper ʻOn the Geometry of Four-dimensions and the Relationship Between Metabolism and Body Mass' (Blum 1977).

critical camps concerning WBE, see 'Complexity a Guided Tour' (Mitchell 2009) and Metabolic scaling: Consensus or Controversy? (Agutter,Wheatley 2004). Having said this however, abstractions and generalizations are necessary in developing inter-theoretic models and it should be clear that the model is an 'average' of general characteristics and not homomorphic to any real network. After all, we commonly refer to the parabolic trajectory of a ball thrown in the air with the understanding that the parabola stops when the ball hits the ground yet mathematically the parabola goes on forever and somewhere the ball is falling still.

4. Conclusion

Allometric economies of scale observed in nature can begin to be understood and explained through consideration of the properties of their fractal distribution and uptake networks. This general notion is an attempt to explain the ubiquity of 1/4 power scaling laws observed so readily in nature. The usefulness of models and simulations, such as WBE and the Netlogo examples here, is not necessarily to glean new insight into any particular examples but to develop a thread of continuity across *all* of biology that sheds some light on essential organizing principles and the tremendous variety and complexity they achieve.
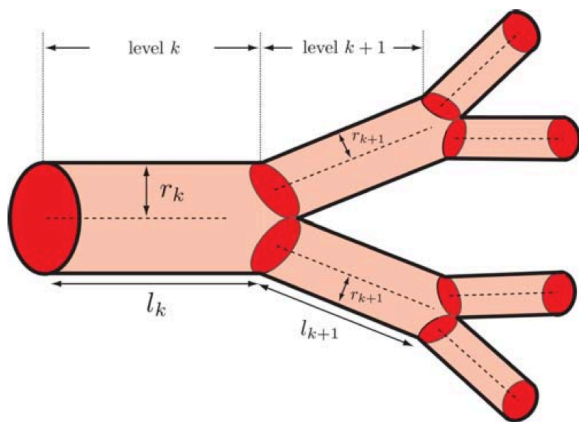
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Appendix: **WBE derivation of 3/4 power law for an averaged fractal network**

M - mass (linearly proportional to volume of blood) $M \alpha V_{blood}$

B - metabolism (linearly proportional to number of invariant terminal units) $B \alpha V_{cap} N_{cap} \alpha N_{cap}$

n - branching ratio. For this model is bifurcating so is = 2

N - number of nodes at a given level k

r_k - radius at a given level

ℓ_k - length at a given level

T - the terminal level in the network, this is the level with capillaries.

$$M \; \alpha \; V_{blood} = \sum_{k=0}^{T} N_k \, \pi \, r_k^2 \, \ell_k \quad \textit{sum of the number of vessels' volumes}$$

$$\pi \, \ell_k \, r_k^2 = \textit{volume of a single tube at level k}$$

$$= \sum_{k=0}^{T} n^k \, \pi \, (\lambda^{-(T-k)} \, \ell_N) \, (\beta^{-2(T-k)} \, r_N^2) \quad \text{※ } \textit{number of vessels}$$

n = 2 for bifurcating network

$$= \pi \, r_T^2 \, \ell_T \sum n^k \quad \lambda^{-(T-k)} \, \beta^{-2(T-k)}$$

volume of a single capillary

$$= n^T V_T \quad \sum n^{-(T-k)} \lambda^{-(T-k)} \, \beta^{-2(T-k)}$$

$N_T = N_{cap} \qquad V_T = V_{cap}$

$$= n^T V_{cap} \; \sum \; 1 / (n \, \lambda \, \beta^2)^{(T-k)} \quad \textit{sum of geometric series}^*$$

$$= V_{cap} \; n^{(4T/3+1/3)} - n^T / n^{1/3} - 1$$

lim as $T \to \infty$ = $n^{4/3}$ *all but leading term drop out*

$$M \; \alpha \; V_{blood} \, \alpha \; V_{cap} \, n^{(4T/3)} \, \alpha \; V_{cap} \, \underbrace{(n^T)^{4/3}}_{N_{cap}} \quad \textit{for } T \to \infty$$

$$M \; \alpha \; V_{blood} \, \alpha \; V_{cap} \; N_{cap}^{4/3}$$

$$M \; \alpha \; V_{blood} \; \alpha \; B^{4/3} \quad \text{because } [B = N_T B_T \text{ (invariant)} \; \alpha \; N_T \; \therefore \; \mathbf{B \; \alpha \; M^{3/4}}$$

Right column:

$$\text{※} \ell_k = (\ell_k / \ell_{k+1}) \, (\ell_{k+1} / \ell_{k+2}) \dots (\ell_{T-1} / \ell_T) \, \ell_T$$
$$(\lambda^{-1}) \qquad (\lambda^{-1}) \dots$$
$$(T-k)$$

$$\ell_k = (\lambda^{-(T-k)}) \, \ell_T$$
$$\lambda = (\ell_{k+1} / \ell_k) = n^{-1/3}$$

$$r_k = (\beta^{-(T-k)}) \, r_T$$
$$\beta = (r_{k+1} / r_k) = n^{-1/2}$$

$$\sum_{k=0}^{T} 1 / (n \, \lambda \, \beta^2)^{(T-k)}$$

let k' = T - k

let x = (n λ β²)⁻¹

$$\sum_{K'=0}^{T} x^{k'} = (n(n^{1/3} n^1)^{-1} = n^{1/3}$$

$$x^{T+1} - 1 / x - 1 \quad \textit{(geometric series)}$$

$$n^{T+1/3} - 1 / n^{1/3} - 1$$