# Origin of Fractal Branching Complexity in the Lung

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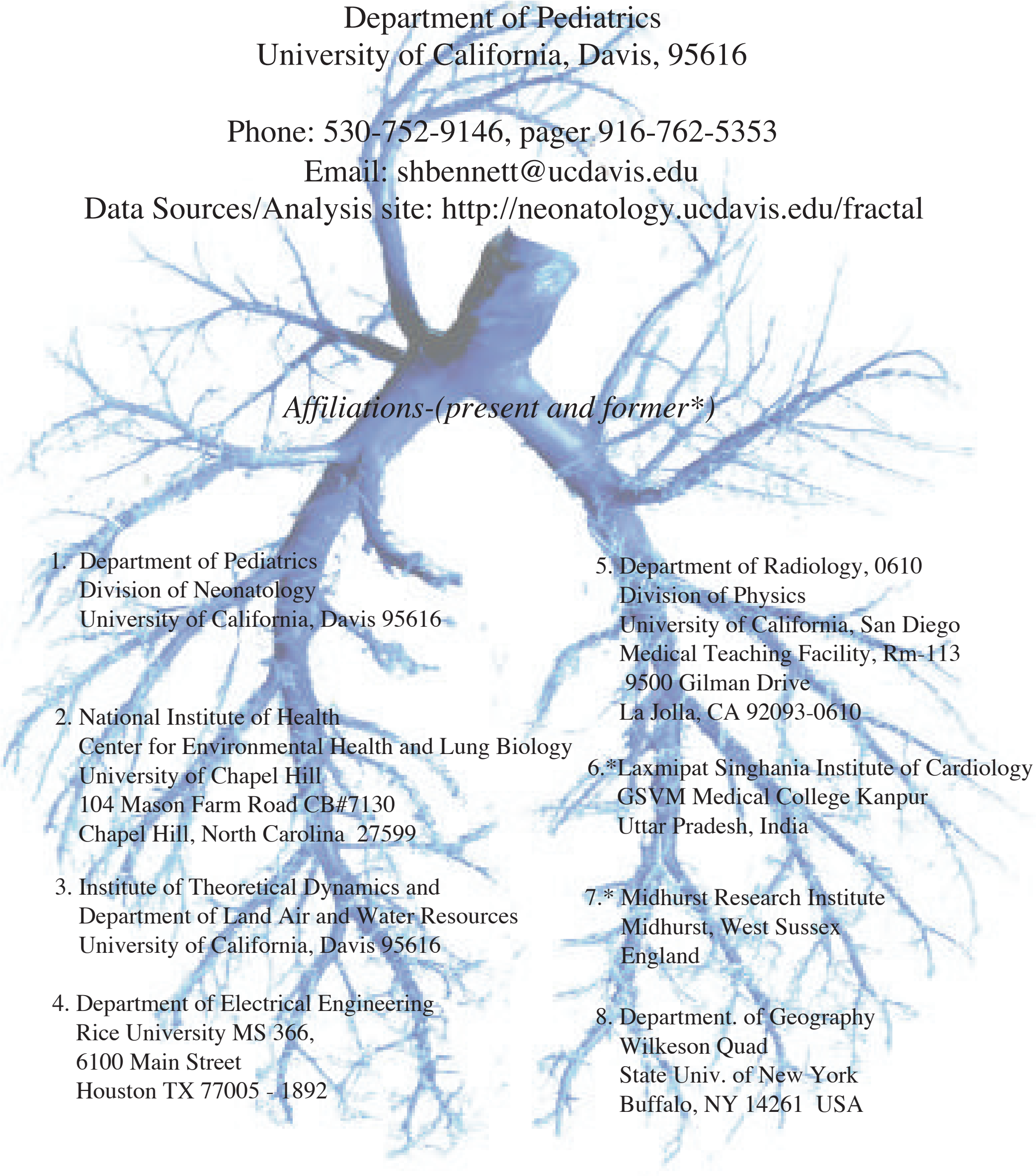

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Fractal and non-fractal theories predict universal designs for biological branching transport networks whereby energy dissipation is minimized. However, they are inadequate to account for adaptation via designs that appear sub-optimal. Therefore we have evaluated another theory in the developing lung which is based on bifurcation design and the principle of self-organized criticality. The latter is a universal physical theory whereby fractal and multifractal patterns of branching complexity self-organize into meta-stable states poised between order and disorder. We find bifurcation design in the lung manifests an adaptable fractal dimension, with spatial scaling properties implicating structural origins of airway and vascular disease susceptibility.

## INTRODUCTION

Branching transport networks in biology form patterns adhering to design principles that are energetically favorable, a condition considered important for species survival(1). Such networks are constructed of vessels via a bifurcating structure, where the parent and daughter vessels, of diameters $d_0$, $d_1$, and $d_2$, respectively, satisfy a bifurcation design relationship $d_0^x = d_1^x + d_2^x$ exhibiting the property of self-organization (2). The bifurcation exponent, x, is said to specify a design because its value reflects the fluid dynamic efficiency and energy dissipation during transport(3). At the network level, an index of design, X, reflects a power-law relationship between vessel number and diameter $N \propto d^{-X}$, where $x \approx X$(4). Although it is not clear to what extent branching complexity implicit in a power law contributes to form and function beyond the vessel level (4-6), both fractal and non-fractal theories of biological network organization predict universal designs with energy dissipation properties at a global minimum or a relative minimum (1,2,7). Not accounted for are biological exceptions, such as the fetal and neonatal pulmonary arterial circulation where design at birth begins with an unusually unstable form of organization for fluid transport(8). A premise of universal theories is that the end design is static, being independent of influences from the environment and unaffected by the functional requirements during development. However, not fully anticipated in current theory, is that the embryonic form of design may metamorphose into a final form during growth and development, in which the early form may satisfy quite different criteria than the final, juvenile or adult state(9) and where patterns and timing of adaptation during successive developmental stages may be just as important for species survival, as the final design(10). In this regard, present theories of biological design are limited in extent because they do no offer explanations for adaptation or mal-adaptation via transitional forms of organization, only the achievement of an idealized final teleological design(1,2,7,9).

In his tome *On Growth and Form*, D'Arcy Wentworth Thompson envisioned a universal principle governing the development and adaptation of form (9) that may have a foundation in a recently proposed physical theory called self-organized criticality(11). This theory postulates a universal process of fractal pattern formation for self-organizing fluid transport networks in nature predicting adaptable patterns of complexity not accounted for in present fractal and non-fractal theories of biological network design(12-13). For example, present fractal theory of biological branching form is based upon the principle of self-similarity where the condition of x=X, results in a space-filling fractal structure, such that x=X=D is predicted to be fixed, emerging early in development(7). However, biological systems do not necessarily exhibit a singular power-law with a design that is universal (4), nor are power-laws of biological branching networks scale-invariant, a condition necessary for self-similarity(14). At present, the fractal architecture of biological networks is an unresolved controversial conjecture, making it unclear as to whether any form of fractal dimension characterizes biological network design(15, 16). Alternatively, a non-fractal theory predicts that biological networks are unorganized stochastic network of bifurcations whose overall function is unaffected by network scaling, being determined by geometric properties residing at the vessel level only(1, 2). Design universality is characterized by a prevailing network average of x coinciding with a global minimum or relative minimum of energy dissipation(3). However, one universal feature of biological networks not accounted for a universal theory is the manifestation of a broad non-normal distribution of bifurcation designs for which a simple average does not necessarily characterize the population uniquely (4,5,8). As large proportions about the average deviate from ideal principles it is not known if the phenomenon is simply biological variation or is related to the optimization of some alternative global cost function related to bifurcation design (3). Alternatively, aberrations not accounted for by universal theories are predicted to be dynamic elements of complexity in a self-organized critical state(12, 17-19), In attempting to build upon Thompson's vision, more vital is the notion that self-organized criticality does not end with an ideal teleological design, but begins with a universal process underpinning design formation, development and adaptation that would lead to possible explanations of diversity and uniformity in biological form.

The case for a fractal self-organized criticality model in biological transport networks is compelling. First, fractal forms of branching are widespread in nature and are advantageous for transport because such forms optimize energy dissipation relative to other patterns(13). Second, self-organized criticality(11-12) represents a plausible theory of fractal pattern formation of import in explaining the process of biological network adaptation(9). Rather than an *a priori* assumption regarding universal fractal design, a self-organized critical state postulates a universal organizational configuration of fractal branching complexity residing in a marginally stable state, possibly far removed from a global minimum of energy dissipation(12). This theory incorporates additional patterns of branching complexity, such as multifractal branching (13) and self-affine fractal scaling(12,14) where the effect of complexity is to break symmetry and impart network scaling properties that spatially modulate forces in self-organization (13). For complexity to emerge, criticality requires the presence of a coupled feedback process to ensure a steady state for which a system is marginally stable against a disturbance (12). Universal patterns are postulated to develop when two types of feedback processes are coupled, one threshold-dependent, the other threshold-independent, (17-19). The coupled process is general so that different transport systems, biological or non-living, can form universal patterns of complexity by different mechanisms(20). Consequently, where non-living transport systems develop over eons of time via a punctuated distribution of forces(13), biological pattern development depends upon the critical timing of information expression, constrained forces and indirect environmental circumstances (21). Hence, for biological networks, self-organized criticality conceives design as a complex adaptive process containing a continuum of physical transitional states with universal patterns of complexity appearing at all stages of development(22). Consequently, this theory would be expected to exhibit locally emergent fractal scaling behavior, giving insight into a network organizational process modulating physiological adaptation and mal-adaptation, rather than a universal fractal dimension.

The mammalian lung is an example of a self-organizing biological branching transport network where conclusive evidence discriminating between a simple-fractal, a complex-fractal or a non-fractal theory is lacking. We will formalize fractal branching complexity, generalizing self-similar and self-affine scaling in power-law behavior, along with patterns of branching for fractal and non-fractal design in biological trees, using a dimension defined according to bifurcation design, x. From this formulation, alternative theories of biological network organization will be tested in the transport vessels of the lung pulmonary arteries and airways, evaluated by assessing the multifractal spectrum inherent in the power-law behavior, wherein the spectra of non-fractal, mononfractal and multifractal branching processes can be assessed(23).

## PATTERNS OF COMPLEXITY IN A SELF-ORGANIZED CRITICAL STATE.

Structural complexity in a self-organized critical state is distinguished by the absence of a characteristic scale(11,12) representing a design objective that minimizes entropy and energy dissipation for a given metastable state (13). In transport networks in nature, structural complexity translates into asymmetric branching patterns modeled via a two-scale Cantorian branching process (12,24). Disorder is patterned through symmetry-breaking properties, leaving a branching structure devoid of a characteristic diameter scale, a characteristic bifurcation design and a characteristic fractal dimension (12, 17-19). Order is reflected via the respective fractal scaling of the symmetry breaking properties in the branching hierarchy. For biological networks we first characterize fractal scaling of network asymmetry by a self-similar fractal dimension based on bifurcation design x(3). A self-similar multifractal spatial distribution forms the basis for breaking the symmetry of bifurcation design within a tree(17-19, 23). However, in contrast to conventional fractal design theory, where scaling principles are assumed to be strictly self-similar, fractal design in fluid transport networks residing in a self-organized critical state include self-affine scaling(12, 14). With self-affine scaling, the fractal and multifractal dimensions change with branching generation when viewed from different perspectives, such as global and local regional scales(14, 16). This latter condition is of consequence to biological networks. At fine-grained diameter scales, changes in slope imply regional adaptations or mal-adaptations in branching design, not evident when viewed at a coarse-grained diameter scale. While these conditions formalize complexity in a branching structure in a critical state, and lead to complicated power-law behavior, they are sufficiently general to include self-similar fractal and non-fractal theories of universal design as special cases.

### *Bifurcation design.*

Transport vessels carrying a flow, Q, branch by asymmetric bifurcation and possess a local symmetry-breaking architecture with a design related to their diameter. In a bifurcation the design, x, of the vessels is related to branching architecture and geometry on the basis of a relationship between parent ($d_0$) and daughter diameters ($d_1$, $d_2$) where , $d_0 > d_1 \geq d_2$,

$$d_0^x = d_1^x + d_2^x \qquad (1)$$

In biological vessels, such as arteries, diameters adhere dynamically to the condition $Q \propto d^x$ where flow conservation condition $Q_0 = Q_1 + Q_2$ holds (3, 20). Bifurcation architecture is conventionally summarized in terms of a diameter ratio, $R_d = d_0/d_1$ and asymmetry ratio, $\gamma = d_2/d_1$. Scaling exponents, x, measured in networks characterize alternative theoretical design principles for a bifurcation which govern its fluid dynamic efficiency(3). The possible range of x is $0 < x < \infty$. However, the measured physiological range is smaller and include values of x=2, 3, and 4(1- 3, 20). In theory, these values form distinctive geometrical constraints for conserving or optimizing geometry and/or fluid dynamic properties in parent and daughter vessels (3). Design conservation principles between parent and daughter vessels occur at certain values of x, with x=2 matching surface area, x=3 represents Murray's law (1), here matching fluid volume; and x=4 matches fluid conductance.. Under conditions of laminar flow these designs have potential physiological significance in that they conserve fluid velocity (x=2), shear stress plus hydraulic power (x=3) and pressure drop (x=4). In mammalian arteries, shear stress is considered an essential control element of design in both fractal and non-fractal theory(1, 3, 20) where the local coupling between shear stress as a threshold-dependent force and wall-stress as a threshold-independent force may constitute elements of two feedback mechanisms leading to a critical state (12, 20). The condition x=3 represents a stable flow condition(1), where energy dissipation and shear stress with flow are minimum. For x<3, flow is marginally unstable, with potential amplification of shear rates in daughter vessels relative to the parent(24). For x<2, an unstable flow condition, the area ratio of the bifurcation is less than one, and both flow velocity and shear stress are amplified in the daughter vessels. In this schema, maintaining constant shear stress requires the limitation of flow to below a critical threshold (9).

### *Fractal dimension based on bifurcation design*

Bifurcation design has been thought as forming the basis of a fractal dimension in branching trees as generations increase to infinity(7). Asymmetric branching in biological networks (25) is analogous to a two-scale Cantorian branching process (23), with the parent diameter, $d_0$, of equation 1 as the initiator and the two dissimilar daughter diameters represent the generators of the process (Figure 1). In generation n, there are $N=2^n$ vessels. Branching to the left results is the major diameter pathway where vessel diameters scale according to $R_d^{-n}$, while the minor diameter branching on the right, scales with each generation according to $gR_d^{-n}$. Within a generation there are $\binom{n}{k}$ vessels with diameter $R_d^{-k}\left(\gamma R_d^{-1}\right)^{n-k}$ spanning from k=0,1,…,n. To formally define the fractal dimension, a measure $M_x$ is constructed, where

$$M_x = \sum_{k=0}^{n}\binom{n}{k} R_d^{-kx}\left(\gamma R_d^{-1}\right)^{(n-k)x} = \left(R_d^{-x} + \left(\gamma R_d^{-1}\right)^{x}\right)^{n} \tag{2}$$

As $n \to \infty$ the diameter scale $\left(\gamma R_d^{-1}\right)^{n} \to 0$, such that $M_x$ remains finite if and only if x=$D_0$, where $D_0$ satisfies

$$R_d^{-D_0} + \left(\gamma R_d^{-1}\right)^{D_0} = 1 \tag{3}$$

This limit defines a network design $D_0$ based on a bifurcation design x in terms of a Hausdorff-Besicovitch dimension. This branching process is said to be monofractal, lacking a characteristic diameter with generation, but exhibits order with branching through the fractal scaling relationship, $D_0$, $R_d$ and $\gamma R_d^{-1}$. While x is an index conveying a design related to fluid dynamic efficiency (3), its convergence to a fractal dimension should not be confused with or identified with a topological dimension related to space-filling properties, except in the limit when branching design becomes space-filling(7, 15-16).

Asymmetric fractal branching leads to a power-law relationship between a branching ratio $R_b$, and the diameter ratio $R_d$ (25) The number of branches, N, as a function of diameter d, with each generation, g, is a self-similar recursive function

$$N_g(d) = N_{g-1}\left(dR_d^{-1}\right) + N_{g-(1+\Delta)}\left(d\gamma R_d^{-1}\right). \tag{4}$$

D, introduced by Horsfield (25), accounts for the degree of asymmetry in numbers between daughter vessels and takes on integer values, such that D=0 reduces to a symmetrical branching tree and integers D>0 introduce successively greater degrees of asymmetry with branching. A branching ratio, $R_b$ is determined from a single iteration of the branching process if the limiting diameter at the termination is known to be fractal. The ratio of successive values of $N_g$, is $R_b = N_g / N_{g-1}$ and when substituted into Eq. 4, gives $R_b^{-(1+\Delta)} + R_b^{-1} = 1$, with one real positive root for $R_b$. Denoting, $R_M$=$R_b$ and $R_m = R_M^{1+\Delta}$, such that ($R_m \geq 2$) and ($1 < R_M \leq 2$), we obtain two alternative forms of the same underlying power-law

$$R_M = R_d^{D_0} \tag{5}$$

$$R_m = R_d^{(1+\Delta)D_0} \tag{6}$$

where $\gamma = R_d^{-\Delta}$ and $R_m^{-1} + R_M^{-1} = 1$. Equation 5 and 6 are alternative scaling interpretations of self-similarity in power-law behavior dependent on a mono-fractal bifurcation design, x=X=$D_0$. The slopes of the power-laws are both equal to x=$D_0$ but indicate different diameter scaling along the major and minor branching pathways. Equation 5 defines a fine-grain diameter scaling of the power-law, where $R_d$ leads to an $R_M$ such that $(1 < R_M \leq 2)$. Equation 6 defines a coarse-grain diameter scaling of the power-law, where $\gamma R_d^{-1} >$ $R_d$ yields $R_m \geq 2$. These branching relationships account for linear self-similar power-law behavior only, whereas power-laws with log-periodic branching can be observed. Such alternative behavior can be accounted for by a complex-valued fractal dimension(27).

Conversely, self-similar power-law behavior in biological networks corresponds to a fractal branching process having two network interpretations. Eqs. 5 and 6 correspond to two classes of equivalent branching networks (14), which imply different connective properties in shaping the forces involved in self-organization (4). Fine-grained diameter scaling, ($R_d$ with $R_M <$ 2) represents the connective branching properties of an equivalent *asymmetric* bifurcating network with a constant D(27). Alternatively, coarse-grained diameter scaling (ɡ $R_d^{-1}$ with $R_m > 2$) represents the branching properties of an equivalent *symmetric* non-bifurcating branching network without connectivity, possessing fewer generations than the related asymmetric network for the same range of diameters (14). There are several methods for summarizing the connective and non-connective branching properties, $R_d$, $R_m$, $R_M$ and $X=D_0$ in biological branching networks. Such methods are useful, but artificial, being based on different topological approaches for vessel classification, such as the Horsfield ($R_M \approx R_H < 2$) and the Strahler ($R_m \approx R_S > 2$), or on ranking schemas(26). If the underlying branching process is a strictly self-similar branching fractal, then it does not matter what method is used to characterize $X=D_0$ (14). However, biological branching networks do not branch indefinitely (7), nor necessarily with the same bifurcation design filling space(4, 7). Therefore, the nature of the power-law behavior is not sufficient evidence of a fractal condition(15, 16). Also necessary for establishing a fractal condition is either evidence of self-similarity in scale-invariant linear power-law or a self-affine scaling condition in a non-linear scale-varying power-law(14). Such conditions are evaluated via a convergence test, accomplished by the evaluation of the multifractal spectrum (Figure 1) which tests for a fractal or non-fractal condition in the limit as branching becomes infinite (23).

### *Multifractal basis of bifurcation design.*

A mono-fractal network is not necessarily an optimal form that minimizes energy dissipation in fluid transport(17-19) and does not account for the observation that bifurcation design in biological networks exhibits a distribution of values(4-5, 8). An additional symmetry-breaking form of structural organization found in branching transport networks in non-living systems in a self-organized critical state includes mutifractal scaling(17-19). The branching structure of Eq. 2 becomes multifractal under slightly different scaling conditions, leading to a tree lacking a characteristic bifurcation design within a generation, but manifests order via a spatial distribution of bifurcation design exponents, analogous to x, defined in terms of a Hausdorff-Besicovitch dimension(23). Symmetry-breaking of the bifurcation design in the asymmetric mono-fractal network is introduced by an additional scaling relationship between $\gamma$ and R$_d$, apart from the Horsfield scaling condition (25) $R_m = R_M^{1+\Delta}$, such that $\gamma = R_d^{-\bar{\Delta}}$, where $\bar{\Delta} \geq 0$, is a constant, here called a Woldenberg delta(28), where $\bar{\Delta} \neq \Delta$. A multifractal distribution is classically expressed in terms of a distribution of fractal dimensions with statistical moment q, ranging from $-\infty < q < \infty$ in three related senses(24): as a distribution of critical exponents $\tau$(q), as a generalized set of fractal dimensions, D$_q$; and of interest here, a multifractal spectrum, f($\alpha$) vs $\alpha$, which relates to the spatial distribution of $\alpha$, where $\alpha$, is analogous to singular spatially determined values x, and f($\alpha$) corresponds to its density distribution.

In a multifractal branching network bifurcations posses critical exponents x=$\tau$(q) where

$$p_0^q l_0^{\tau(q)} + p_1^q l_1^{\tau(q)} = 1 \qquad (7)$$

such that $\tau$(q) is a member of an underlying distribution function indexed by the moment q, Here, l$_1$ and l$_2$ (l$_2$>l$_1$) are the diameter contraction ratios ( $l_1 = \gamma R_d^{-1}$ and $l_2 = R_d^{-1}$) in the minor and major daughter branches of a bifurcation where R$_d$ and $\gamma$ are defined above. The terms p$_1$, p$_2$ (p$_2$>p$_1$) are defined in terms of R$_m$ and R$_M$, where $p_1 = R_m^{-1} \leq \frac{1}{2}$, $p_2 = 1 - p_1 = R_M^{-1} \geq \frac{1}{2}$, and are associated with diameter contraction ratios l$_1$ and l$_2$. If Equation 7 is considered a generator in a branching process, we can subsequently define a measure in a manner similar to Eq. 2 above,

$$M_x = \left(p_1^q l_1^x + p_2^q l_2^x\right)^n = \sum_{k=0}^{n} \binom{n}{k} p_1^{kq} p_2^{(n-k)q} l_1^{k\tau} l_2^{(n-k)\tau} = 1 \qquad (8)$$

It is clear that as the number of generations $n \to \infty$ , M$_x$ remains bounded for the choice of x=$\tau$(q), $M_x \to 0$ for a bifurcation scaling exponent $x > \tau(q)$, while $M_x \to \infty$ for $x < \tau(q)$. This condition makes $\tau$(q) a critical exponent. In the multifractal formalism, $\tau$(q) is related to a distribution of fractal dimensions $D_q = \tau(q)/(1-q)$ for an infinite set of moments q over $-\infty < q < \infty$, bounded by $D_{-\infty} > D_0 > D_\infty$. The distribution D$_q$ has characteristic fractal dimensions related to specific moments q: for q=0, D$_0$ is the fractal dimension of design support as in Eq. 3; for q=1, D$_1$ is the information dimension; and for q=2, D$_2$ is the correlation dimension. Our interest is in another distribution called the singularity spectrum, f($\alpha$), which is the Legendre transform of $\tau(q)$, that is $f(\alpha)=\min\big(q\alpha+\tau(q)\big)$ and $\tau(q)=\max\big(f(\alpha)-a\alpha\big)$. The value of q which minimizes $q\alpha+\tau(q)$ is the one in which $\alpha=-\tau'(q)$ where the prime indicates the derivative. Here, q serves as a natural parameter indexing $\alpha$ and f in which $\alpha$ is bounded between $\alpha_{\min}=D_{\infty}$ and $\alpha_{\max}=D_{-\infty}$. Now, the parameter $\alpha$ is an exponent measuring the strength of singularity or degree of unbalance of branching at a location within the branching process. The expression $f(\alpha)$ is the corresponding fractal density, indicating how large a part of the whole branching tree possesses this singularity of degree $\alpha$, where the singularity strength of $\alpha$ within a generation n is approximately $2^{nf(\alpha)}$.

Figure 1 illustrates multifractal spectra for a monofractal branching process compared to multifractal branching process. The multifractal branching network pattern illustrates one possible configuration with a simple form of spatial clustering of scaling exponents $\alpha(\varepsilon)$ within the major and minor pathways leading to the indicated convex spectra. The spatial properties of $\alpha$ are specified as a position index $\varepsilon$, where $\varepsilon = k/n$ and $0\le\varepsilon\le 1$ in the branching process of Eq. 8. Here, $\alpha(\varepsilon)$ are diameter scaling exponents analogous to x in Eq. 1, but are now singular values in a multifractal distribution whose values range from $\alpha_{\min}$ to $\alpha_{\max}$, and whose value within the network depends upon bifurcation position defined by $\varepsilon$ in the binomial expansion of Eq. 8. The density spectrum of $\alpha(\varepsilon)$ is a limit probability distribution, $f(\varepsilon)$, as the order of branching becomes large,

$$f(\varepsilon)=\frac{H(\varepsilon)}{(1+\Delta\varepsilon)\ln R_d} \tag{9}$$

such that $H(\varepsilon)=\varepsilon\ln\varepsilon+(1-\varepsilon)\ln(1-\varepsilon)$ is the entropy distribution function of statistical mechanics and is convex in shape reaching a maximum of 1 at $\varepsilon=1/2$. The relative magnitude of $\overline{\Delta}$ and $\Delta$ influences the range of extreme values of $\alpha$

$$\alpha(0)=\frac{\ln R_M}{\ln R_d} \tag{10}$$

$$\alpha(1)=\frac{1+\Delta}{1+\overline{\Delta}}\alpha(0) \tag{11}$$

The density $f(\alpha(\tfrac{1}{2}))$, corresponding to $\varepsilon=1/2$, is simply the fractal dimension of the support related to the moment q=0, specified by $f(\alpha(\tfrac{1}{2}))=D_0$ .

A power law does not convey whether an underlying branching process is multifractal and the power-laws implied by a branching process converging to a convex multifractal spectrum are not simple. The generalized fine-grained and coarse-grained power laws in multifractal branching are of the form

$$R_M^{(1+\Delta\varepsilon)/\left(1+\bar{\Delta}\varepsilon\right)} = R_d^{\alpha(\varepsilon)} \qquad (12)$$

$$R_m = R_d^{\alpha(\varepsilon)\left(1+\bar{\Delta}\varepsilon\right)} \qquad (13)$$

where symmetry-breaking emerges under conditions of $\Delta \neq \bar{\Delta}$ but reduces to a mono-fractal branching architecture when $D=\bar{\Delta}$, and where $D$ and $\bar{\Delta}$ no longer are restricted to integer values. There are an infinite number of power-laws according to the range of $e$, but power laws analogous to Eq. 5 and 6 are obtained by setting $e=1/2$where the slope of the power-law is equal to $D_0$, the same result for the monofractal branching condition. However, unlike monofractal branching, a multifractal configuration imparts a spatial distribution of bifurcation cross-sectional area capable of modulating the fluid dynamic forces involved in self-organization(29). The power-laws in Eq. 12 and 13 are linear but can have log-periodic variations if $D_0$ is a complex-valued fractal dimension(27), or be self-affine(14). Consequently, a multifractal branching condition is verified via the computation of the multifractal spectrum and its convergence to a convex spectrum(23, 30).

*Self-affine fractal scaling of bifurcation design*

An additional property serving to break symmetry in a self-organized critical branching network is to modify the form of fractal scaling in the branching process, from a self-similar scale-invariant state, as assumed in present simple-fractal branching theory, to a self-affine form of scaling, which is scale-varying(12, 14). Under these circumstances, the fractal dimension $D_0$ varies continuously with the branching region of interest. Consequently, non-linear power-laws arise, one form which may appear piece-wise linear, under fine-grained diameter scales, a property found in the power-laws of lung airways and pulmonary arteries(14). A verification of a fractal self-affine condition, as opposed to the branching process not being fractal, is established by evidence of dissimilar convergent multifractal spectra over different regions of branching where the slope of the local power-law becomes the local regional fractal design of support, $D_0$(23).

A departure from a self-similar scaling condition leads to locally emergent behavior in branching properties for biological networks. Self-affine scaling of bifurcation design is expected and necessary for a physiological branching network to adjust its bifurcation design, x, toward a value of 3 as branching becomes space-filling in exchange vessels (7, 16). In a self-affine condition, the global scaling properties of fractal design, which characterize the energy dissipation in a marginal stable state (12) are now disassociated from the scaling properties responsible for the modulating the distribution of forces involved in self-organization(4). This disassociation implies that spatially varying designs are present throughout a branching tree while the global power-law appears unchanged at a coarse-grained diameter scale. Consequently, self-affine scaling potentially identifies hidden regional network scaling adaptations at fine-grained diameter scales, where fractal design shifts away from ideal bifurcation behavior of x=3 or ideal power-law behavior of X=3. Also, self-affine scaling eliminates the possibility that a branching network exhibits a universal design with characteristic energy dissipation properties(1,7).

## Complexity versus Universal design in the lung

While one cannot mathematically prove fractal behavior in limited branching networks (15), one can alternatively assess conclusive evidence of the presence or absence of a convergence criterion as branching becomes infinite via the evaluation of the multifractal spectrum(23, 30). Therefore, testing for fractal complexity versus universality was evaluated by comparing power-laws and multifractal spectra in the lung airways (31) and developing pulmonary arterial system (8,32) using fine-grained and coarse-grained diameter scales.

### *Complexity in the fetal/neonatal pulmonary arterial circulation*

One of the most dramatic physiological adaptations made by a biological transport network in nature occurs at birth in the mammalian pulmonary vascular system after the first breath (10, 33). The lung in the fetus is a dormant organ with a high resistance, requiring a small level of blood flow for development. Arterial vessels have made structural adaptations to a physiologically high pressure that is never again experienced postnatally, except under extreme exercise conditions, or disease states(34). After the first breath of life, lung airway expansion is accompanied by an arterial network transition from a high-pressure, low-flow network to a lower-pressure, high-flow system(10, 33). While the distribution of x in the fetal and neonatal pulmonary circulation is unknown, Thompson argues that a starting working hypothesis would be based on the principle of minimum work in bifurcation design, where x=3(1, 9). Consequently, this would imply that the high resistance to blood flow in the fetal arterial system is dictated by humoral factors constricting vessel diameters, whereby the diameters increase with flow and shear-stress dependent factors along with lung expansion after birth(33). However, a phenomenon not explained at this stage of development, is an unusual susceptibility to flow-induced vascular injury when relatively modest elevations in blood flow above a threshold occur, yielding additional structural modifications in arteries leading to complications in adaptation at birth(34).

Hopkins theorized that structural or mechanical factors within the pulmonary circulation cause the perinatal arterial network to posses a different profile of energy dissipation than that of a mature pulmonary arterial system(35). A corollary hypothesis is a self-organized critical interpretation, predicting that the arterial design is in a metastable state, possibly far removed from a global minimum of energy dissipation of $x<3$.

Figure 2 represents three theoretical views of bifurcation design in a fetal lamb (140 days/145 days at term) Fig 2ACE, and a 1 day-old neonatal lamb, Fig 2BDF, representing the structural state, just prior to, and just after birth(8). Figure 2A and 2B represents the distribution of bifurcation design exponents, x, for the fetus and newborn, calculated for each bifurcation in the lung calculated according to Eq. 1. The gray area in Fig 2AB and 2EF marks those bifurcations with a design condition of $x<2$, an unstable condition for flow transport, indicative of an area-ratio, $b<1$. The figure indicates that a significant proportion does not adhere to ideal principles, but does not reveal where they are located or how they are scaled with branching. Fig 2CD represents the corresponding power-laws at a coarse-grained (squares) and fine-grained (circles) scaling of diameter. The red, blue and green colors correspond to the slopes of regional power-laws indicative of the condition $x=X$ in different regions of the lung relative to the main pulmonary artery feeding the arterial system: globally, proximally and distally, respectively. The changes in slope do not identify whether the system is non-fractal, or possesses a complex-valued fractal dimension (28), or if the fractal branching is self-similar or self-affine. The fine-grained diameter scaling power-law in Figure 2CD suggests that the location of bifurcations with values of $x<2$ in Fig 2A and 2B are located distally as one branches outward towards smaller vessels. Figure 2EF represents the evaluation of the fetal and neonatal multifractal spectra and the emergence of complexity from Figure 2AB and 2CD. The colors in Fig 2EF mark regions of branching corresponding to the power-laws of C and D where the slopes of the power-laws are equal to the peaks of the corresponding multifractal spectra. As a convex spectrum represents a multfractral branching process as one approaches an infinite branching limit, one concludes that the underlying distribution of bifurcation design is multifractal, as such a condition would not have arisen had the branching process been simply stochastic or strictly self-similar being characterized by a unique dimension(23). That a different multifractal condition is present in other branching regions implies that the branching process is self-affine, not strictly self-similar(14).

These results indicate that in the higher pulmonary resistance state of the fetal and neonatal pulmonary circulation, the larger pulmonary arteries do not follow universal biological design principles of x=2 or 3, instead exhibit fractal branching complexity in a metastable state of marginal stability far removed from a global minimum of energy dissipation(12). After birth, there is an adaptation of design, regions shifting globally and locally toward higher values, but remain far removed from a universal minimum of x=3. It is important to emphasize that at a fine grained level of diameter scaling, the proximal and distal regions in the fetus and newborn show disparities in design with the distal arteries with a more severe decrease in cross-sectional area. The design in the distal region of both fetus and newborn represents a bottleneck of decreasing cross-sectional area with branching, where shear stress associated with blood flow is amplified as it progresses toward the periphery(4). Above a threshold, shear stress associated with blood flow is capable of inducing a chain of events occurring over different time-scales, leading to changes in the force-transduction properties of the endothelial wall(20) and the integrity of vessel structure and function, with large increases in flow consequently producing injury(34). The unusual bifurcation design of x<2, along with the branching complexity inherent in the structural organization of the fetal and neonatal pulmonary circulation therefore explains a basis for Hopkin's theory of dissipation and for the unusual susceptibility of the perinatal pulmonary circulation to injury from elevated blood flow(35)

### *Complexity of Adult Human Pulmonary Arterial Circulation*

While the developmental patterns of arterial branching complexity in the pulmonary circulation are not known, adulthood is expected to adhere to a universal design (1, 2, 7) as an adaptation of design that is more efficient than the fetal and newborn state (10). However, while a universal design prescribes an allometric scaling of resistance at a fixed flow rate commensurate with body weight (7), such a theory is inadequate in predicting the variations in resistance between individuals over a wide range of flows, as experienced at rest and extreme exercise(36). For an unknown reason, some individuals, including highly trained athletes, have highly elevated resistances above the expected universal norm and are fatally susceptible to consequences of pulmonary hypertension under extreme environmental and exercise conditions (36-37). Analogous to the fetus and newborn pulmonary circulation, the susceptibility is hypothesized to have structural and/or humoral origins(35). A universal design hypothesis for the pulmonary circulation implies that a self-similar fractal dimension will be observed (7) while a complexity hypothesis can implicate a design variation that is apparent only at fine-grain diameter scales.

Figure 3ACE represents a fractal analysis of an adult human pulmonary vascular system free of pulmonary vascular disease (32) expressed in the same format as Figure 2. In Fig 3A, the distribution of bifurcation design exhibits a large proportion of values less than 2, consistent with local decreases in bifurcation cross-sectional area with branching. Fig 3C demonstrates that, similar to the fetus and newborn state, regional self-affine scaling of fractal design is evident when viewed from fine-grained diameter scales. In Figure 3E, the convergent multifractal spectra with different fractal dimensions of support are found in different regions of arterial branching, indicating that the network branching design scales in a self-affine manner. In Fig3E, the distal branching indicates a regional instability of decreasing cross-sectional area where $x<2$, a condition similar to that found in the fetal and newborn state. Such a decrease in cross-sectional area, not detectable from a coarse-grained view of diameter scaling represents a persistence of the fetal design and a possible structural origin of susceptibility, analogous to the fetal condition of blood flow injury secondary to elevated shear stress and blood flow(354-35).

### *Complexity of Adult Human airways*

The laws of lung development (38) dictate that the airway branching pattern is laid down prior to the arterial vascular branching pattern, and the latter arises from the airways before blood flow and shear stress can contribute to such a process (7). However, as the previous results suggest, arterial design adapts dramatically during development and growth, but airway branching power-laws are consistent with Murray's law of $x=X\approx 3$ at birth (39) indicating a different process of design development. Under a universal design hypothesis, a self-similar monofractal design of $x=3$ expected to be present. Alternatively, under a self-organized critical hypothesis, the complexity of the airways is expected to give rise to complexity in the arterial system where both lack a characteristic fractal dimension of design.

Figure 3BDF summarizes the branching analysis for the airways. Fig. 3B illustrates a greater proportion of bifurcations around $x=3$. Figure 3D shows linear power-law behavior close to $x=X=3$ for coarse-grained diameter scales, but with additional slope changes with fine-grained scaling. Figure 3F, is the multifractal analysis of airway branching data of an adult human. This figure demonstrates that the airways exhibit branching complexity, with multifractal branching and a self-affine state of fractal scaling, consistent with a system in self-organized critical state(12). While the coarse-grained diameter scaling indicates a design consistent with Murray's law, the fine grained diameter scaling indicates that smaller vessels change their fractal dimension of support with branching. This result shows that the complexity of bifurcation design, laid down early in development, is apparent in the adult airways, and may therefore influence the development of design in arterial pathways as well(10, 38).

## CONCLUSIONS

The design of larger transport vessels in the lung were found to exhibit fractal branching complexity with an origin consistent with systems in nature conforming to a self-organized critical state. The changes complexty in the pulmonary circulation are dynamic suggesting that the lung is a complex adaptive system lacking a lacking a universal fractal design, and is not a strictly self-similar branching network. Also, there is evidence of a fractal self-affine form of scaling, implicating a structural organizational source of vascular disease susceptibility. However, while such complexity appears to account for much of the bifurcation design variation in the lung, it is not apparently responsible for all possible patterns seen in branching morphogensis (40), therefore, should not be considered the only process governing biological branching pattern formation. Alternatively, a self-organized critical state may be part of a universal pattern of biological network development, growth and adaptation. Even with this limitation, fractal branching complexity of a self-organized critical network may obviate the concept of a universal design (1, 2, 7), remaining consistent with universal biological design principles (41) while providing a theoretical framework for understanding the process of biological network adaptation (9,10).

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14. Liinear power-laws such as $N \propto d^{-X}$ conform to self-similar fractal behavior if they are scale-invariant satisfying the scaling relationship $N(d) = R_d^{-X} N\left(R_d^{-1} d\right)$ where $R_d$ is a diameter ratio greater than one. A simple test illustrating the absence of scale-invariance involves comparing power-law behavior in the same biological branching network under two topological conditions of vessel ordering,, such as the Strahler and Horsfield method [K. Horsfield in *The Lung: Scientific Foundations* R. Crystal and J. West Ed. (Raven, New York, 1997), chap 75, pp 1073-727]. The Strahler method characteristically yields linear power-laws with fewer orders of branching under a coarse-grained diameter scaling, or large $R_d$ with vessel number. However, the Horsfield method, which scales diameter in a fine-grained manner with a smaller $R_d$ more orders of vessels, produces piece-wise linear plots with different slopes. A strictly self-similar fractal network would yield identical linear power-laws with the same slope regardless of the method of ordering or scaling. Consequently, the system may not be fractal be at all, or alternatively, posses a fractal scaling property that is self-affine, with non-linear power-laws that are scale-varying possessing local and global fractal dimensions depending upon the scale of view[J Feder, *Fractals* (Plenum Press New York 1988)]. Of interest to adaptation is fractal self-affine with different dimensions of design within different regions of branching.
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27. According to renormalization group theory, fractal scaling of the form $N(d) = R_d^{-D} N\left(R_d^{-1} d\right)$ between vessel number N and diameter d has a complex valued fractal dimension as one of its solutions [MF Shlesinger, BJ West, *Phys Rev Lett* **67**:2106 (1991)]. The general form of the fractal dimension becomes $D_0 = |D_0|\cos\phi + i|D_0|\sin\phi = X_r + iX_i$, where $\phi$ is a phase angle and $i = \sqrt{-1}$. In the case of the two-scale self-similar branching process, this condition leads to log-periodic variations in the power-laws, $R_M^n = R_d^{nX_r}\left(1 + A\cos\left(2\pi n X_i \ln R_d\right)\right)$ and $R_m^n = R_d^{n(1+\Delta)X_r}\left(1 + A\cos\left(2\pi n(1+\Delta)X_i \ln R_d\right)\right)$. The constant, A, is the amplitude of oscillation in the power-law with the imaginary component of the fractal dimension, $X_i$, determining the frequency of oscillation with generation n. These equations are scale-invariant: a change in diameter scaling, via a fine-grained or coarse-grained $R_d$ will maintain the same linear power-law slope $X_r$, and amplitude A, but alter the apparent frequency of oscillation. Log-periodic behavior is found in the airway branching of several species of animals and consists of two trends [B.J. West, V Bhargava A.L. Goldberger *J Appl Physiol* **60**:1089(1986); T.R. Nelson, B.J West and A.L. Goldberger *Experientia* **4** 251 (1990)]. A global linear trend is appears to impart a universal aspect of scaling common to all fractal networks whereas the variations about the linear trend has been interpreted as containing individual and species-specific information pertaining to regional diameter scaling. However, it is not known if the underlying log-periodic power-laws in biological networks are scale-invariant, and therefore fractal in a self-similar sense.
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30. Evidence of a multi-fractal branching process is established by a necessary convergence condition to a limit probability distribution appearing as a convex spectrum with touch [C.J.G. Evertsz and B.B Mandelbrot in *Chaos and Fractals* H.O. Peitgen, H Jurgens, D. Saupe (Springer-Verlag, New York, 1992) Appendix B pp 921-953]. Method of spectrum determination was based on A. Chhabra and R.V. Jensen *Phys Rev Lett* **62** 1327 (1989); lung branching data sets for diameter $d_i$ were decimated for coarse-graining by sorting from largest diameter $d_0$ according to orders k=0, 1…n by $d_0 R_d^{-k} \geq d_i > d_0 R_d^{-(k+1)}$ Where $R_d$ is a provisional diameter ratio used as a ruler such that $R_d \approx 1.15\text{-}1.3$. At coarse-grained diameter scales, ie larger $R_d$, the number of generations was limited to approximate linear power-law behavior in relationship $\ln R_{bk} vs \ln R_{dk}$, where $R_{bk}=N_k/N_0$ corresponds to generation determined by average diameter $R_{dk}=\bar{d}_k/d_0$ per generation k. The measure used in multi-spectral method was $\mu_1 = d_i \big/ \sum d_j$, and $\mu_i^q = d_i^q \big/ \sum d_j^q$ for spectral moments where $d_i \in$ inclusive order from 0 to k at scale $\delta_k = R_d^{-k}$. Spectral values at a given moment, q, were determined by f(q), as linear the regression of $\sum_{i\in k}^{n} \mu_{k,i}^q \ln \mu_{k,i}^q \ vs \ \ln \delta_k$ and $\alpha(q)$ as the linear regression of $\sum_{i\in k}^{n} \mu_{k,i}^q \ln \mu_{k,i} \ vs \ \ln \delta_k$ both ranging over diameter scales of interest according to order $\delta_k$ from k to n. A convergent spectra implies that a branching region of interest is consistent with the connective properties of an equivalent branching network of the form specified in Eqs 7 and 8 in the text and the configuration in Figure 1.
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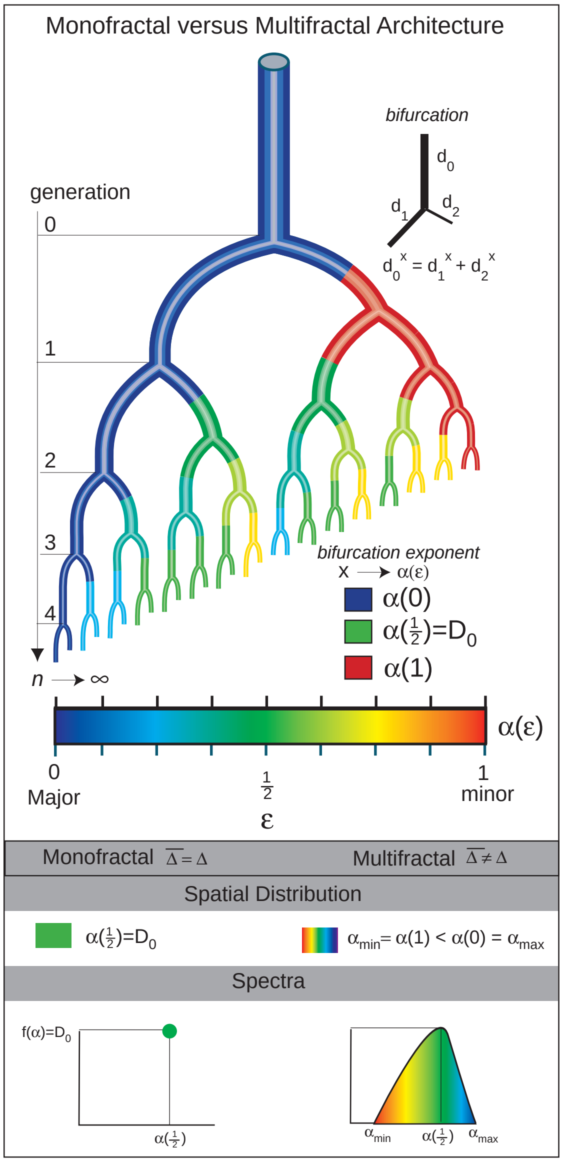
**Figure 1. Architecture of a branching network**. Alternative theories of biological network design predict different consequences for the scaling and distribution of bifurcation design x in relationship $d_0^x = d_1^x + d_2^x$ in trees. Consequences manifest themselves in the spatial distribution of x within branching tree, and in the appearance of multifractal spectrum, f(a) versus a, which tests convergence to a limit probability distribution of branching structures with limited generations as branching becomes infinite. Non-fractal theories predict x is distributed randomly without scaling relationships, monofractal theory predicts identical distribution of x in tree. Self-organized critical state predicts a multifractal scaling relationship spatially distributing x in network along with a self-affine scaling of the fractal dimension with generation.

*Bifurcation design x*: Between parent and daughter vessels, the exponent x dictates fluid dynamic efficiency of fluid transport and cross-sectional area with branching: x=2 is constant fluid velocity with the preservation of cross-sectional area; x=3 is Murray's law corresponding to constant fluid volume with constant hydraulic power; and x=4 represents constant fluid resistance with preservation of pressure drop. For values x<2 cross-sectional area of bifurcation decreases, a condition resulting in amplification of flow velocity and shear stress, forces participating in vessel self-organization.

*Multifractal branching* condition represents one aspect of branching complexity inherent in a self-organized critical state. Branching condition involves symmetry-breaking of mono-fractal pattern into a spatial distribution of scaling exponents such that $x \to \alpha(\varepsilon)$, where a(e) is a singular distribution of bifurcation exponents distributed with branching according to address e, where 0<e<1, Density of a(e) is given by f(a(e)) in multifractal spectrum. Condition e=0 marks bifurcation exponent a(0) along major daughter pathway e=0, and e=1 marks bifurcation exponent a(1) along minor daughter pathway. Fractal dimension of support for bifurcation design is designated by $\varepsilon = \frac{1}{2}$ where $\alpha\left(\frac{1}{2}\right) = D_0$. Address of bifurcation a(e) in tree is determined by index k and n of binomial expansion of Equation 7 in text. In figure a(e) is distributed over a range of values $a_{min}$ to $a_{max}$. encoded with colors of rainbow. If $a_{min}$=a(0) of major diameter pathway, then minor pathway must possess condition $a_{max}$=a(1) and vice-versa. Control of distribution of scaling exponents a(e) and shape of multifractal spectrum, is via the terms $\Delta$ and $\overline{\Delta}$, called the Horsfield and Woldenberg delta in text.

*Self-similar versus Self-affine fractal scaling of bifurcation design:* The scaling of $D_0$ with branching is different in the three theories. Non-fractal theories do not exhibit scaling properties, hence no fractal dimension. Universal fractal theories presuppose the fractal scaling is self-similar, leading to conditon of scale-invariance of design throughout branching tree and strictly linear power-laws. Complexity interpretation predicts multifractal branching plus self-affine fractal scaling whereby the $D_0$ varies from one generation to another leading to non-linear power-laws.



Monofractal versus Multifractal Architecture

**Figure 2. Fetal and Neonatal Ovine Arterial System.** Three scaling views of bifurcation design in fetal and neonatal pulmonary circulation where branching architecture does not adhere to idealized design principles of x=3: AB-distribution of x as if a stochastic branching network. CD-power law behavior for different regions of branching, EF-multifractal spectra of branching as a network in a self-organized critical state. Data from (8).

AB-*Distribution of bifurcation design in tree:* Bifurcation design, x, in each bifurcation solved according to $d_0^x = d_1^x + d_2^x$ where 0 is parent diameter, 1 is major daughter and 2 is minor daughter. Area ratio, `b` is sum of squares of daughter vessels divided by square of parent area. Grey area marks bifurcations with area ratio<1. **Fetus** (N=2844 bifurcations where bifurcation = 3 vessels). Fetal mean values of x: arithmetic mean=2.076; geometric mean=1.684; harmonic mean =1.50. Fetal mean values `b`: arithmetic mean=0.8573; geometric mean=0.811; harmonic mean 0.753. **Newborn** (N=812 bifurcations). Newborn mean values of x: arithmetic mean=3.44;geometric mean=2.059; harmonic mean=1.453. Newborn mean values of `b`: arithmetic mean=0.944; geometric mean=0.767; harmonic mean 0.469

CD-*Power-law behavior of distribution in AB:* Underlying distribution of bifurcation exponents exhibits a non-linear power-law behavior suggesting that branching is a self-similar fractal with a complex-valued fractal dimension predicting log-periodic behavior that is scale-invariant. Non-linear interpretation draws slopes in proximal and distal regions for sake of comparing with global design. Coarse-grained ($R_{dc}$=squares) and fine-grained ($R_{df}$=circles) decimation of diameter in bifurcations were used to form corresponding power-law relationships, $R_m^n = R_{dc}^{nX}$ and $R_M^n = R_{df}^{nX}$ with equal slopes = X (colored red) where n denotes generation starting from n=0 for largest vessels inceasing in index towards smaller vessels. Coarse graining with diameter scale $R_{dc}$ yields an equivalent symmetric branching network without bifurcation connectivity having a branching ratio $R_m=R_b>2$. Fine-graining with diameter scale $R_{df}$ yields equivalent asymmetric branching network with bifurcation connectivity having $R_M=R_b<2$. **Fetus**: branching properties $R_{df}$=1.33, :$R_{dc}$=2.152; $R_M$=1.51; $R_m$=3.0. **Newborn:** branching properties $R_{df}$=1.32, $R_{dc}$=1.613, $R_M$=1.66, $R_m$=2.52. **Fetus**: values of power-law slopes X: *Red*-global X=1.43;*Blue*-proximal=1.994;*Gree*n-distal=0.939. **Newborn**: values of power-law slopes X: *Red*-global =1.79;*Blue*-proximal=2.44;*Gree*n-distal=1.40.

EF-*Multifractal Spectra of power-law behavior in CD*: Convergence to convex multifractal spectrum in proximal and distal regions evidence of self-affine fractal scaling with each local $D_0$ equal to local slopes X. A global view of branching is colored red with superimposed multifractal spectra: symmetric branching-coarse grained(boxes) and asymmetric-fine grained (circles). Proximal region colored blue and Distal region colored green. While regions were chosen arbitrarily to compare larger versus smaller vessels in branching, any combination of branching regions chosen manifest multifractal branching designs, indicating that the fractal dimension of support $D_0$ scales continuously with generation. Results support theory that branching architecture is in a self-organized critical state where complexity in branching yields a global design minimized for energy dissipation but varies local design without a characteristic design, to modulate forces of self-organization throughout tree.

*Figure 2.Ovine Fetal and Neonatal Pulmonary Arterial Systems*

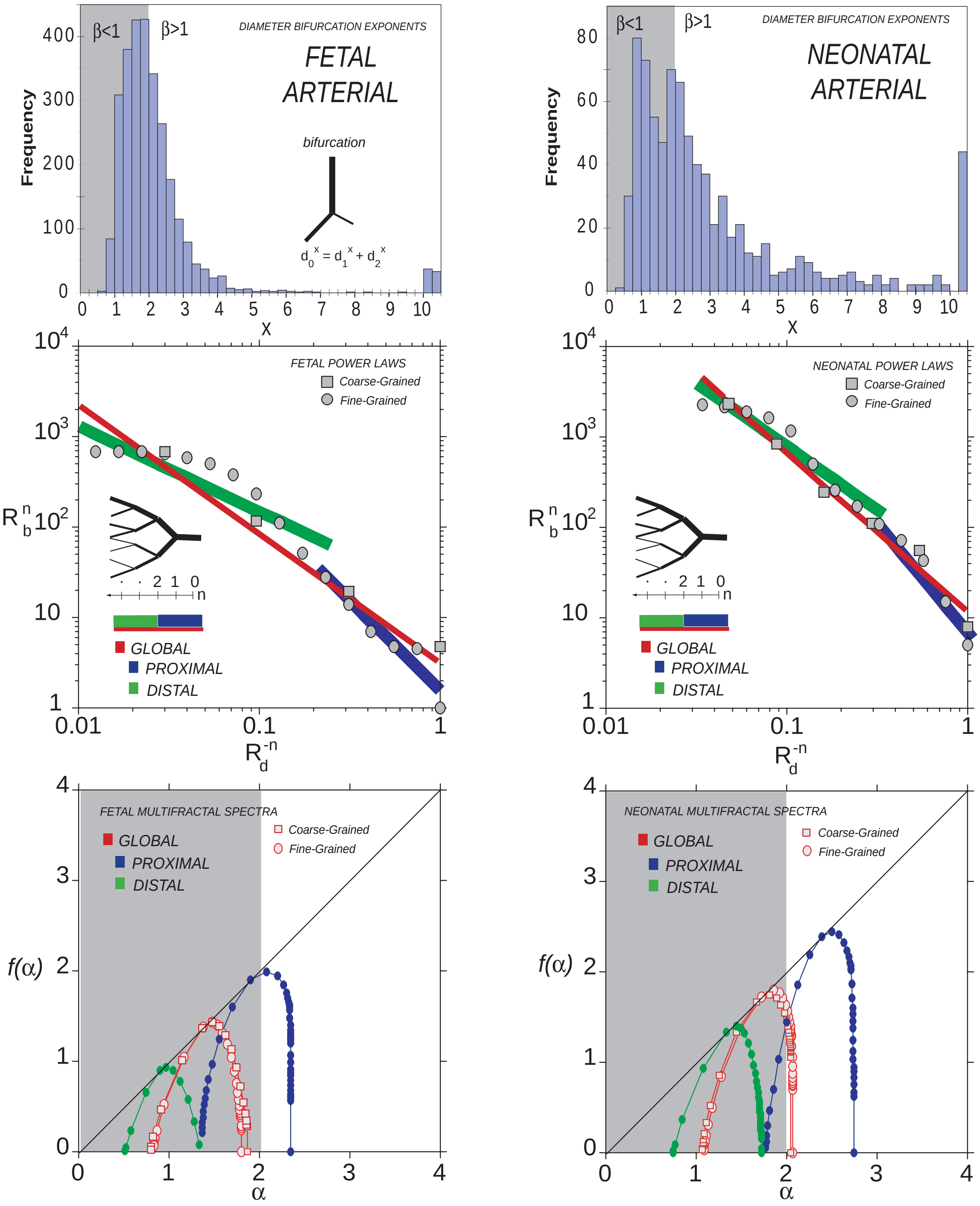


**Figure 3. Human Pulmonary Arterial (ACE) and Airway System (BDF)**. Pulmonary arterial system branching is known to arise from branching morphogenesis of airways. Stochastic bifurcation design theory and mono-fractal theory predict fixed designs at x=3 or x=2 in larger transport vessels. Theory of Self-organized critical state predicts complexity of arterial system is found in complexity of airways, but not necessarily with the same design or scaling.

***Arterial System-***(ACE)-data from S.S Singhal, R, Henderson, K. Harding and G, Cumming *Circ Res* **33** 190 (1973). N=893 bifurcations

A-*Distribution of x and* b. Grey area marks bifurcations with area ratio b<1. Mean values of x: Arithmetic mean=2.33, geometric mean =2.23; harmonic mean=2.12. Mean values of b: arithmetic mean=1.063; geometric mean=1.045; harmonic mean=1.025

C-*Power-law behavior of distribution in A:* As in Figure 2, coarse-grained ($R_{dc}$=squares) and fine-grained ($R_{df}$=circles) decimation of diameters in bifurcations were used to form corresponding global power-law relationships, $R_m^n = R_{dc}^{nX}$ and $R_M^n = R_{df}^{nX}$ with equal slopes = X (colored red)=2.39. Global arterial branching properties $R_{df}$=1.33, :$R_{dc}$=2.152; $R_M$=1.51; $R_m$=3.0. At fine-grained decimation, power-law exhibits changes in power-law slope suggestive of a change in fractal design. Value of slopes: X=Proximal branching-(blue)=2.62, X=Distal (green)=1.81. Distal region implicates decreasing cross-sectional area with branching where non-ideal bifurcation designs reside as a population, similar to what was observed in fetus and newborn lamb.

E-*Multifractal Spectra of power-law behavior in C:* Convergence to convex pectrum globally, proximally and distally, is evidence that underlying fractal dimension is self-affine multifractal consistent with structure in a self-organized critical state. The global view of branching (red) as a multifractal network can also be viewed as two branching processes with successive fractal designs proximal and distal. The distal design does not adhere to ideal design principles and appears to be a developmental remnant of fetal state.

***Airway System-***(BDF)-data from K. Horsfield, *J Appl Physiol* 24 373 (1968) N=2613 bifurcations

B-*Distribution of x and* b. Mean values of x: Arithmetic mean=2.78, geometric mean =2.53; harmonic mean= 2.35. Mean values of b: arithmetic mean=1.124; geometric mean=1.102; harmonic mean=1.079

D-*Power-law behavior of distribution in A:* As in Figure 2, coarse-grained ($R_{dc}$=squares) and fine-grained ($R_{df}$=circles) decimation of diameters in bifurcations were used to form corresponding global power-law relationships, $R_m = R_{dc}^X$ and $R_M = R_{df}^X$ with equal slopes = X (colored red)=3.1. Global arterial branching properties $R_{df}$=1.157, :$R_{dc}$=1.387; $R_M$=1.59; $R_m$=2.7. At fine-grained decimation, power-law exhibits changes in power-law slope suggestive of a change in fractal design. Value of slopes: X=Proximal branching-(blue)=3.0, X=Distal (green)=2.51. Distal region has significantly different design of power-law behavior than proximal region.

F-*Multifractal Spectra of power-law behavior in C:* Convergence to convex spectra globally, proximally and distally, in airways is evidence that underlying branching network is a self-affine multifractal consistent with structure in a self-organized critical state. The complexity of the airways appears related to the complexity of the arterial branching.

*Figure 3.Human Pulmonary Arterial and Airway Systems*