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The concept of symmorphosis: A testable hypothesis of structure–function relationship

(respiratory system/mitochondria/capillaries/maximal oxygen consumption)

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ABSTRACT **The hypothesis that, in biological organisms, structural design is matched to functional demand is difficult to test because it is largely based on anecdotal evidence suggesting economic design. The hypothesis of symmorphosis postulates a quantitative match of design and function parameters within a defined functional system; because of its stringency it is refutable and can, therefore, be subjected to empirical test, for example, by assessing whether the structures that support the pathway for oxygen from the lung to the consumer in muscle cells are quantitatively adjusted to the limit of functional performance of the respiratory system. The study of allometric and adaptive variation leads to the conclusion that the hypothesis of symmorphosis is acceptable for all internal compartments of the respiratory system (blood, heart, muscle capillaries, and mitochondria), whereas it must be refuted for the lung that forms the interface to the environment.**

The concept that animals, and humans as well, should be designed economically (i.e., that structural design should be matched to functional demand) follows from common sense, but it is also supported by many observations. Thus blood vessel architecture is such that blood flow distribution occurs with minimal energy loss; bone structure is patterned according to stress distribution and also quantitatively adapted to total stress; with training, athletes can specifically adjust the structure of their muscles and of their cardiovascular system to higher functional demands, and these modifications are soon reversed when training is stopped. These examples suggest optimization of structural design based on the cost-to-benefit relationship: the larger an organ the more it will cost in terms of construction, maintenance, and load on the body. Most of this evidence is anecdotal, however, and one can come up with similar anecdotal evidence that questions this conclusion.

To test the validity of the concept of economic design as an important principle of structure–function relationship in biology requires a hypothesis that postulates a quantitative match between parameters of design and function. This appears fulfilled by the hypothesis of symmorphosis, defined as the state of structural design resulting from morphogenesis regulated to match functional demand (1). From this hypothesis we would predict that, if the functional requirements on an organ system vary, structural design should vary in parallel.

Symmorphosis has recently been discussed from various aspects (2–4). We wish to summarize the insight we have gained in studying the mammalian respiratory system and the morphometric variations that accompany varying functional demands.

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The Respiratory System and Symmorphosis

The respiratory system of mammals is a good test case for the hypothesis of symmorphosis for a number of reasons.

(*i*) It serves one dominant overall function, the supply of O_2 from environmental air to the mitochondria in the cells in support of oxidative phosphorylation.

(*ii*) This overall function has a measurable limit, the aerobic capacity or maximal rate of O_2 consumption, $\dot{V}O_{2max}$.

(*iii*) This functional limit varies between individuals and species.

(*iv*) The respiratory system involves a sequence of structures: the lung, the blood, the heart, microcirculation, and the mitochondria in (muscle) cells, which all need coadjustment when aerobic capacity is varied.

(*v*) At each step a number of functional parameters are involved that can be rapidly adjusted, whereas the structural parameters are "fixed" quantities that are very slow in adapting (days to months) and thus potentially set the capacity of the system for instantaneous functional performance.

The model of the respiratory system shown in Fig. 1 breaks the pathway for O_2 into four steps (5–7): two steps of diffusive gas exchange in the lung and in the peripheral microvasculature are connected by the convective transport of O_2 by circulation of the blood; the final step represents the consumption of O_2 in the process of oxidative phosphorylation in the mitochondria. Under steady-state conditions, the flow of O_2 through each of these steps is equal to $\dot{V}O_2$ measured at the mouth.

The functional and the structural parameters that affect the transfer functions at every step are identified in Fig. 1 where the functional factors are shown to the left and the structural factors are to the right of the central multiplication dot. The product of the factors shown in boldface type determine $\dot{V}O_2$ directly; the parameters shown in italic type within braces are determinants of these factors. These equations will be discussed step by step below.

Testing the Hypothesis of Symmorphosis by Comparative Physiology

The test of the hypothesis is to set the morphometric measurements into relation to the physiological variables pertinent for each transfer step and, particularly, to $\dot{V}O_{2max}$ as the overall estimate of aerobic capacity. The simplest question to ask is how the variables vary with changes in $\dot{V}O_{2max}$. Alternatively, the hypothesis of symmorphosis predicts that the design parameters form an invariant ratio with $\dot{V}O_{2max}$ under all modes of variation, if the morphometric features are linked with aerobic capacity.

The test we propose is based on the study of variations of $\dot{V}O_{2max}$ between animals or species. The approach we have

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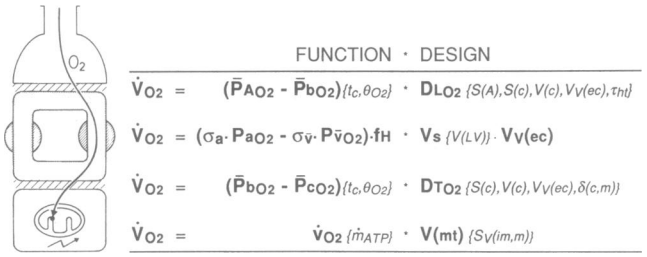

FIG. 1. Model of the respiratory system. The O_2 flow rate $\dot{V}O_2$ is expressed as the product of functional and design parameters shown in boldface type; parameters that affect the factors are shown in italic type and placed in braces. The functional parameters include: O_2 partial pressures PO_2, coefficients of "hematocrit-specific" O_2 capacitance σ that depend on O_2–hemoglobin dissociation, O_2 binding rate θ, heart frequency fH, capillary transit time t_c, and mitochondrial O_2 consumption rate as function of ATP flux $\dot{v}O_2\{\dot{m}_{ATP}\}$. Design parameters include: diffusion conductances D of lung and tissue gas exchangers that depend on alveolar and capillary exchange surface areas S(A) and S(c), respectively, capillary volumes V(c), hematocrit V_V(ec), harmonic mean barrier thickness τ_{ht}, capillary–mitochondrial diffusion distance δ(c,m), and mitochondrial volume V(mt) with inner membrane surface density S_V(im,m).

chosen is to use comparative biology, for it is well known that metabolic rate and also maximal O_2 consumption vary considerably between species, mainly for the following two reasons.

(*i*) *Allometric Variation.* Differences in body mass, M_b, cause $\dot{V}O_{2max}/M_b$ to be more than 5 times higher in a mouse than in a cow because metabolic rate is proportional to about $M_b^{-0.2}$ (8–10).

(*ii*) *Adaptive Variation.* Animals of similar size can be adapted to different levels of endurance performance; dogs and horses can be considered to be endurance athletes as they achieve a $\dot{V}O_{2max}$ that is 2.5 times higher than that of sedentary species of their size class such as goats and cows (11).

These variations have different causes: the differences observed in adaptive variation relate to behavioral traits and to the ecological conditions to which the species are adapted by evolutionary selection perhaps reinforced by domestication and breeding selection; in contrast, allometric variation reflects intrinsic properties of the organism, particularly, the size dependence of rate constants, such as stride frequency, heart rate, etc. (10). We can therefore expect the different functional and structural parameters of the respiratory system (Fig. 1) to react differently with these two types of variation.

In testing the hypothesis of symmorphosis we use, as basic reference parameter, maximal O_2 consumption, $\dot{V}O_{2max}$, with the argument that this should reveal "bottlenecks" and redundancies in the pathway. $\dot{V}O_{2max}$ is measured while the animal is running (12); under these conditions more than 90% of the O_2 consumption occurs in the skeletal muscle cells, and in quadrupedal animals a major fraction of the skeletal muscle mass is engaged in locomotion so that the body compartment serving as the major O_2 sink is clearly identified, whereas in bipedal locomotion of the human this may be different (13). The physiological studies require measurements of the most important functional variables, such as cardiac output and blood gas tensions, at $\dot{V}O_{2max}$ (11). The morphometric study is designed to obtain measurements of all structural parameters considered relevant (Fig. 1) in muscle, heart, and lung, using reliable stereological methods and sampling strategies that allow whole body data to be calculated (11). We have done three sets of experiments of this kind, one dealing with allometric variation (6) and two comparing three species pairs showing adaptive variation (11, 14–16).

Muscle Mitochondria and $\dot{V}O_{2max}$

The last equation in Fig. 1 defines the O_2 flow rate into the O_2 sink as the product of total mitochondrial volume of muscle V(mt) with the O_2 consumption rate of the unit volume of mitochondria $\dot{v}O_2$(mt). This simple relation is justified by the observation that the respiratory chain enzymes are densely built into the inner mitochondrial membranes and that their surface area within the unit volume of mitochondria is invariant at about 35 $\mu m^2/\mu m^3$ both in different skeletal muscle types and in different species (17–19).

Since time is a fundamental variable in allometric variation, we would expect $\dot{v}O_2$(mt) to vary directly with $\dot{V}O_{2max}/M_b$ in animals of different size. The hypothesis of symmorphosis would then predict that V(mt)/M_b should be invariant in allometric variation. In adaptive variation we would, in contrast, expect $\dot{v}O_2$(mt) to be invariant whereas mitochondrial volume should be matched to O_2 consumption. As shown in Fig. 2 and Table 1, this is not what we found (19, 21): in both adaptive and allometric variation V(mt)/M_b varied in strict proportion to $\dot{V}O_{2max}/M_b$ with the result that $\dot{v}O_2$(mt) was invariant at 4–5 ml of O_2 per min irrespective of size or state of adaptation of the animal (25).

At the level of the mitochondrial O_2 sink in skeletal muscle the invariant ratio of morphometric parameter to $\dot{V}O_{2max}$ is, therefore, simply

$$[V(mt)]/\dot{V}O_{2max} = 0.2[ml(mito)]/(ml\ of\ O_2\ per\ min)$$
$$= invariant,$$

under all circumstances of the test. We thus conclude that the amount of mitochondria stands in direct relationship to $\dot{V}O_{2max}$ and thus determines oxidative capacity. If a muscle needs more capacity for oxidative phosphorylation, it builds more mitochondria of the same kind.

Muscle Capillaries and O_2 Delivery to Mitochondria

The diffusion of O_2 from capillaries to the mitochondria is determined by a PO_2 difference as driving force, and a diffusion conductance, DT_{O_2}, that contains all the design

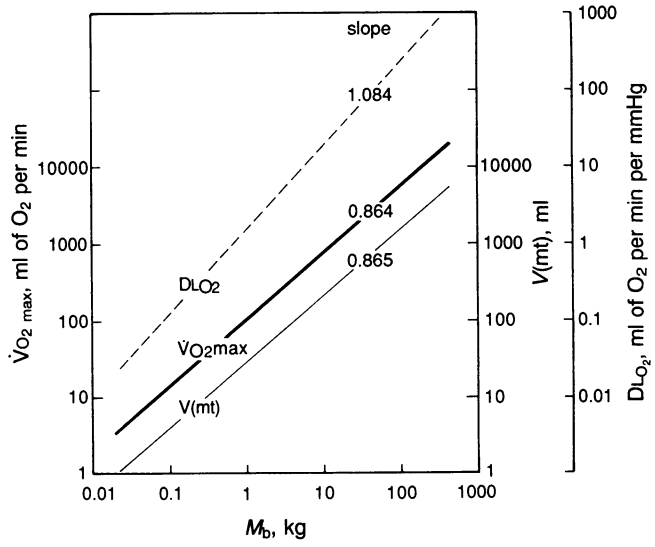

FIG. 2. When plotted logarithmically against body mass $\dot{V}O_{2max}$ and whole-body muscle mitochondrial volume V(mt) have nearly equal slopes whereas that for pulmonary diffusing capacity DL_{O_2} is clearly different. The regression equations (with M_b in kg) are $\dot{V}O_{2max} = 106.8\ M_b^{0.864}$ (units, ml of O_2 per min; 95% confidence interval for slope, 0.752–0.980); $V(mt) = 30.1\ M_b^{0.865}$ (ml; 0.804–0.926); $DL_{O_2} = 1.55\ M_b^{1.084}$ (ml of O_2 per min per mmHg; 0.895–1.272). Data are from refs. 6, 8, 19, and 20.

Table 1. Differences in morphometric and physiologic parameters of muscle mitochondria and capillaries and of heart, blood, and lung with adaptive variation of $\dot{V}O_{2max}$ in three athletic/sedentary pairs

		Mitochondria		Blood	Capillaries		Heart			Lung	
	$\{\dot{V}O_{2max}/M_b\}$, ml·sec^{-1}·kg^{-1}	$[V(mt)/M_b]$, ml/kg	$[V(mt)]/\{\dot{V}O_{2max}\}$, ml·ml^{-1}· sec	$[V_V(ec)]$, %	$[V(c)/M_b]$, ml/kg	$[V(c)\cdot V_V(ec)]/\{\dot{V}O_{2max}\}$, ml·ml^{-1}· sec	{fH}, min^{-1}	$[V_S/M_b]$, ml/kg	$[V_S\cdot V_V(ec)]/\{\dot{V}O_{2max}/fH\}$, ml/ml	$[D_{L_{O_2}}/M_b]$, ml·sec^{-1}· mmHg^{-1}·kg^{-1}	$[D_{L_{O_2}}]/\{\dot{V}O_{2max}\}$, mmHg
25–30 kg											
Dog (D)	2.29	40.6	17.7	0.50	8.2	1.79	274	3.17	3.16	0.118	0.052
Goat (G)	0.95	13.8	14.5	0.30	4.5	1.42	268	2.07	2.92	0.080	0.084
Ratio D/G	2.4*	2.9*	**1.2**	1.68*	1.8*	**1.26**	1.02	1.53*	**1.08**	1.48*	**0.61***
150 kg											
Pony (P)	1.48	19.5	13.2	0.42	5.1	1.45	215	2.50	2.54	0.079	0.053
Calf (C)	0.61	9.2	15.1	0.31	3.2	1.63	213	1.78	3.21	0.050	0.082
Ratio P/C	2.4*	2.13*	**0.9**	1.35*	1.6*	**0.89**	1.02	1.40*	**0.79**	1.57*	**0.65***
450 kg											
Horse (H)	2.23	30.0	13.5	0.55	8.3	2.05	202	3.11	2.58	0.108	0.048
Steer (S)	0.85	11.6	13.7	0.40	5.3	2.49	216	1.52	2.58	0.054	0.064
Ratio H/S	2.6*	2.6*	**1.0**	1.4*	1.6*	**0.82**	0.94	2.1*	**1.00**	2.0*	**0.76***
Ath/Sed	**2.5***	**2.5***	**1.03**	**1.5***	**1.7***	**0.99**	**1.0**	**1.7***	**0.96**	**1.7***	**0.67***

Functional parameters are set in braces. Design parameters are set in brackets. Boldface numbers are adaptive pair ratios for the design/functional parameters. The last line presents overall ratios for athletic/sedentary (Ath/Sed) species. Data are from refs. 11, 14–16, and 21–24.
*Ratios significantly different from 1.

parameters that affect O_2 diffusion, capillary volume $V(c)$ and surface $S(c)$, and the characteristic diffusion distance to the vicinity of the mitochondria $\delta(c,m)$ (Fig. 1, line 3). The architectural situation is not simple, and a model does not exist for estimating $D_{T_{O_2}}$. However, the basic design pattern of muscle microvasculature is sufficiently similar in different species and muscles that a comparative study of the relation between capillaries and mitochondria can be based on simple estimators of design. Thus capillary volume and surface as well as the radial diffusion distance (radius of Krogh cylinder) are all related to the length density of capillaries in muscle, a quantity that can be estimated reliably (26, 27).

In first approximation, we predict from the hypothesis of symmorphosis that the volume of capillary blood in the muscles is proportional to the muscles' capacity to consume O_2: in individual muscles capillary volume should be proportional to mitochondrial volume, and total muscle capillary volume $V(c)$ should vary directly with $\dot{V}O_{2max}$.

In allometric variation we found that $V(c)/M_b$ varies in direct proportion with $\dot{V}O_{2max}/M_b$ and with weight-specific mitochondrial volume (26). In adaptive variation (22), it was found that athletic species have, paradoxically, a relatively smaller capillary volume than sedentary animals of the same size (Table 1). However, the athletic species were found to have a hematocrit, $V_V(ec)$, about 1.5 times higher than the other species with the result that their blood has a larger O_2 capacity. The product of capillary volume and hematocrit estimates capillary erythrocyte volume; Table 1 shows that the ratio of total capillary erythrocyte volume to $\dot{V}O_{2max}$ is invariant between the species pairs of adaptive variation. In allometric variation there is no systematic trend for differences in hematocrit or hemoglobin concentration.

We therefore conclude that, in both instances, the invariant ratio of capillary parameters to aerobic capacity is

$$[V(c)\cdot V_V(ec)]/\dot{V}O_{2max} \approx [1.8 \text{ ml(ec)}]/(\text{ml of } O_2 \text{ per min}) = \text{invariant}.$$

We note that in this instance two morphometric parameters are involved: the quantity of capillaries and the concentration of O_2 carrying erythrocytes in capillary blood. Thus the microvasculature and the blood contribute about equally to establishing conditions for O_2 supply that are proportional to needs.

Convective O_2 Transport by the Circulation of Blood

The transport of O_2 by the circulation depends on the properties of the heart as the pump and on those of the blood as O_2 carrier as expressed by the Fick equation (Fig. 1, line 2): the arteriovenous O_2 concentration difference is affected by the P_{O_2} in arterial and venous blood, by the hematocrit, and by the O_2 capacitance of the blood, which we have expressed as a "hematocrit-specific" variable σ_{O_2} to separate functional and structural variables. Cardiac output $\dot{Q}$ is the product of a functional parameter, heart frequency f_H, and stroke volume V_s, a structural parameter that is proportional to heart weight (unpublished observations).

On the basis of the hypothesis of symmorphosis, we would predict that the two morphometric parameters, ventricular or stroke volume and hematocrit, should be matched to $\dot{V}O_{2max}$ as the global measure of O_2 transport capacity. Table 1 shows that in adaptive variation the stroke volume of athletic species is about 1.6 times higher than in sedentary species; when considering the differences in hematocrit, we find that the product of erythrocyte volume with stroke volume, what one could call the "erythrocyte stroke volume", is increased in proportion to $\dot{V}O_{2max}$ in the athletic species. It is noteworthy that the maximal heart frequencies are pairwise identical

in the size classes (Table 1). Accordingly, the higher O_2 transport capacity of athletic species is achieved purely by structural adaptation (23).

In allometric variation, heart frequency at rest varies directly with O_2 consumption (5, 9, 10); maximal heart frequency is not sufficiently well documented but, from the data in Table 1, it appears that it should follow about the same allometric regression as resting heart rate. On the other hand, heart weight makes up the same fraction of body mass over the size range of mammals from mouse to cow, namely, 0.58% (28), so that the ratio V_s/M_b should be invariant with body size because we have found V_s to be linearly related to heart mass (unpublished data). Likewise, hemoglobin concentration in blood and hematocrit do not vary systematically with body size (29). Although allometric measurements of circulatory parameters under conditions of $\dot{V}O_{2max}$ are scarce, the available evidence suggests that the size-dependent change in $\dot{V}O_{2max}/M_b$ is matched by a change in the functional parameter heart frequency whereas the structural parameters V_s/M_b and hematocrit are invariant.

We therefore conclude that the prediction derived from the hypothesis of symmorphosis, namely, that stroke volume and hematocrit should match $\dot{V}O_{2max}$, is fulfilled in adaptive variation; in allometric variation, heart frequency comes into play, which, like metabolic rate, is a dominant functional parameter when body size varies. When testing the hypothesis of symmorphosis by seeking an invariant ratio of structural-to-functional parameters, this must be taken into account. We find that

$$[V_s \cdot V_V(ec)]/(\dot{V}O_{2max}/fH_{max}) = 2.8[ml(ec)]/(ml\ of\ O_2) = invariant$$

holds for both adaptive and allometric variation.

Uptake of O_2 in the Lung

The transfer rate of O_2 from the air into the blood (Fig. 1, line 1) is driven by the partial pressure difference from alveolar air to capillary blood, $(P_{A_{O_2}} - P_{b_{O_2}})$, a functional variable that depends on the ventilation of alveoli and the perfusion of capillaries. The conductance or diffusing capacity $D_{L_{O_2}}$, in contrast, is largely determined by structural parameters (7, 30) and has two main components: the membrane diffusing capacity $D_{M_{O_2}}$ depends on the alveolar and capillary surface areas $S(A)$ and $S(c)$ and on the harmonic mean thickness of the tissue and plasma barriers τ_{ht} and τ_{hp}, whereas the capillary blood volume $V(c)$ and the hematocrit, together with the O_2 binding rate coefficient θ_{O_2}, determine the O_2 uptake capacity of the blood.

The hypothesis of symmorphosis predicts that the compound parameter of structural design $D_{L_{O_2}}$ should be proportional to $\dot{V}O_{2max}$. This is not the case. In allometric variation we find that $D_{L_{O_2}}$ has a different slope from $\dot{V}O_{2max}$ when plotted against body mass (Fig. 2) with the result that the ratio $D_{L_{O_2}}/\dot{V}O_{2max}$ increases with $M_b^{0.2}$ (20). Thus a 300-kg cow has six times as much diffusing capacity as a 30-g mouse to accomplish O_2 uptake at $\dot{V}O_{2max}$, so that the driving force for O_2 uptake is smaller in the cow than in the mouse.

In adaptive variation we have found that athletic species have a larger gas exchange surface area and a higher hematocrit than nonathletic animals, which results in a larger $D_{L_{O_2}}/M_b$ in the athletic species (Table 1), but this increase is not proportional to the differences in $\dot{V}O_{2max}/M_b$ (15, 24). When combining physiological measurements with the morphometric estimate of $D_{L_{O_2}}$, we found that capillary transit time t_c was invariant and that all lungs used only a fraction of t_c for equilibration of capillary to alveolar P_{O_2}; but this fraction was greater in athletic species, namely, 80% versus 50% in the sedentary species (31).

In conclusion, we find that the ratio

$$D_{L_{O_2}}/\dot{V}O_{2max} \neq invariant,$$

neither in allometric nor in adaptive variation. As a result the functional parameter $(P_{A_{O_2}} - P_{B_{O_2}}) = \Delta P_{O_2}$ must vary as well because $D_{L_{O_2}}/(\dot{V}O_{2max}/\Delta P_{O_2})$ must be invariant by definition (Fig. 1, line 1). This result leads to the conclusion that the hypothesis of symmorphosis does not apply at the level of the pulmonary gas exchanger.

Discussion

The hypothesis of symmorphosis predicts that structural parameters are matched to functional capacity. We have based the test of this hypothesis on a comparative study of the mammalian respiratory system. We have asked whether the design parameters of the structures that support O_2 flow are matched to the aerobic capacity of the organism estimated by the maximal rate of O_2 consumption, $\dot{V}O_{2max}$, because this is the only condition where we can expect all of the available structure to be utilized. We compared the effects of two types of natural variation in $\dot{V}O_{2max}$, allometric versus adaptive variation, and accepted the test of the hypothesis if the two conditions gave identical results.

This study reveals that it does not make sense to test the hypothesis of symmorphosis on single structural parameters but that the entire structural system must be considered in context. The simplest structure–function relationship was found at the level of the mitochondria where we found the total muscle mitochondrial volume to vary in strict proportion to aerobic capacity; it appears that the molecular constitution of muscle mitochondria is invariant so that a higher capacity for oxidative phosphorylation can only be achieved by building more of the same mitochondria into the muscle cells. At the other levels of the respiratory system, we found that more than one structural parameter could be varied and that this was utilized in varying capacity. Thus, the capacity of the microcirculation to deliver O_2 to the cells can be modified either by increasing the density of the capillaries or by changing the blood composition. Likewise, O_2 transport by the circulation can be increased either by pumping more blood with a bigger heart or by packing more erythrocytes into the blood. Which option is used may depend on economic considerations: increasing the number of erythrocytes per unit blood volume will reduce the amount of blood the heart must pump, but it will, conversely, increase pumping cost due to higher blood viscosity, so that there will be an optimal range of erythrocyte concentration (between 30 and 50%) where pumping cost is minimal (32, 33). In the perspective of symmorphosis it, therefore, appears economic to partition the adaptive effort between the two structural systems, and we found, indeed, that it was the products of the morphometric parameters of vessels and of blood that were proportional to the functional parameter: hematocrit times capillary or heart volume, respectively. That heart frequency must be involved as an additional functional factor in allometric variation of $\dot{V}O_{2max}$ was discussed and justified above: time is a dominant factor when body size changes (10).

When considering all the morphometric parameters of the pulmonary diffusing capacity, we did not find them to be proportional to $\dot{V}O_{2max}$, neither singly nor in combination. It rather appeared that the lung maintains a considerable excess diffusing capacity, up to a factor of 2 in sedentary species, that can be partly exploited in athletic species to achieve higher uptake rates; this also allows sedentary animals to maintain their aerobic capacity in a hypoxic environment (31). We conclude that with the currently available evidence the hypothesis of symmorphosis must be refuted for the pulmonary gas exchanger.

In general conclusion, it appears from this analysis that the principle of economic design, as reflected in the hypothesis of symmorphosis, is upheld for all the internal compartments of the respiratory system, but it does not appear to apply to the lung. Future work will have to address mainly two questions: (*i*) to examine whether symmorphosis as evidenced in this study is indeed related to an economic design principle of minimizing cost and (*ii*) to ask why the pulmonary gas exchanger is different from the other parts of the system—whether it is, for example, because the lung forms the interface to the environment and is, therefore, exposed to additional stresses. The most important question will be to elucidate in other systems whether symmorphosis reflects a basic principle, to which there may be some exceptions, or whether it must be refuted in the end. For the time being this hypothesis still has considerable heuristic value.

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