

Dear Dr. Liebermeister,

Thanks a lot for having taking charge of our manuscript! We also would like to thank the reviewers for their helpful comments that helped us to improve greatly our manuscript.

We took into account all the comments and rewrote many parts of the manuscript in such a way assumptions and previous results are easier to understand. Also, we made the paper easier to read by summarizing the mathematical derivations in the main text and detailing them either in footnotes for short derivations (referenced as citations in the text) or in appendices for more complex derivations.

Biochemical details were corrected and simplified as they are not in the scope of the paper.

Also, we refined some of our results. We give now two distinct behaviors for the localization of the convection-diffusion transition: one in the bronchial tree and one in the acini. The trends are both linear in the logarithm of the mass, but the slopes are slightly different, see equation (6) and Figure 3.

Finally, we reread carefully the paper to improve the English. We hope it is now satisfactory.

In the PDF submited, we wrote in red the major changes made in the manuscript.

Kind regards,
F. Noël, C. Karamaoun, J.A. Dempsey, B. Mauroy.

by Wolfram Liebermeister, 2020-11-16 14:38
Manuscript: <https://arxiv.org/abs/2005.12362>

Suggested revision

Dear authors,

Thank you again for sending us your interesting preprint! I apologize for the long time you had to wait for a response, and thank you for your patience.

Reviewer 1 is very fond of your work, but asks you to restructure your manuscript to improve its readability, and to clarify assumptions and previous results. Reviewer 2 asks for various a number of detail changes and points out biochemical details to be addressed by your revised manuscript.

I find your preprint very interesting, but not always easy to read. The text quite dense and requires a lot of attention on the side of the reader - so like Reviewer 1, I encourage you to move some of the details into a methods or supplement section and to streamline the text to highlight a bit more the most important results. Also, I suggest to have the manuscript checked by a native speaker, since the language is sometimes not perfectly idiomatic.

I am looking forward to a revised version of your preprint.

Thank you again for supporting our PCI!

Sincerely yours, Wolfram Liebermeister

Reviewer 1

In the manuscript "The origin of the allometric scaling of lung's ventilation in mammals", the authors present a model of optimal control of ventilation for the lung to infer the localisation of the transition between convective and diffusive gas transport. Essentially, the model assumes that the energetic cost for gas transport is minimised. An existing model was generalised for mammals of arbitrary size, exploiting previously proposed scaling laws. The results indicate differences between small and large mammals, in particularly showing that in small mammals the screening effect, which denotes the fact that only a part of the lung's surface can be used for gas exchange, is small, under all exercise regimes. In large mammals, this is quite difference, and therefore the transition between convective and diffusive transport changes considerably between base metabolic rate and maximal metabolic rate. Various new scaling laws are derived, including the dependence of the tidal volume and the breathing frequency on the animal's body mass.

The findings are very interesting and, if correct, give considerable new insight into the scaling of transport systems, that may potentially be applicable also to other biological systems, in which transport networks are important.

We thank you for this very positive comment of our paper.

The problem I personally have with the manuscript is that the mathematical derivations are not easily accessible. It is, for example, hard to understand, which assumptions are made, which results have been previously obtained, and then how these assumptions and previous results are used to derive novel scaling laws. Unfortunately, I am unable to rigourously check the mathematical derivations.

Thanks a lot for this remark that helped to improve a lot our manuscript. We rewrote a lot of the text to make the assumptions clearer and to highlight our results.

In the model section, we made clearer the novelty of our model and how it is based on our previous paper Noël and Mauroy, 2019.

Please, see more details in the answers to your following remarks.

In order to accept the manuscript for publication, I therefore suggest that the authors aim at improving in particular the results section. Model assumptions should be clearly stated, listed, and justified. Likewise, results that have been previously obtained, should be more clearly summarised and briefly justified.

We reformulated more clearly the assumptions all throughout the text. Moreover, we synthesized all of them in two tables (IV and V) in Appendix VII.

We added a summary the hypotheses at the beginning of the results section and referenced the tables IV and V in Appendix VII.

I think it would help if the mathematical derivation, including intermediate steps, would be presented in an appendix or supplement, and that in the main paper only the most important and key derivations are presented. Ideally, the logic of the reasoning should be clearly understandable and the key ideas of the mathematical derivation of the central formulas should be explained in the main text, while detailed steps are presented in a supplement, where the interested reader (and reviewer) can follow the single steps.

As suggested, we removed many of the mathematical derivations from the text and replaced them by text explanations and a supplement out of the main text.

In order to avoid having many short appendices, short derivations are presented in footnotes, which are referenced as citations in the revtex template. Referencing footnotes as citations allows to give more details since “normal” footnotes take space on the pages of the paper.

Longer mathematical derivations were also added as appendices, such as the equations on the partial pressure of oxygen (appendix I).

We hope this template will be satisfactory.

Some results, that appear very interesting and worthy of a more in-depth discussion, are mentioned only superficially. For example, the observation that the model fits an allometric scaling law stating that the lung's exchange surface scales with the body mass as $M^{11/12}$ is remarkable. This means that the surface almost scales linearly with body mass. Is this surprising only to me? Are there fractal designs that could push the exponent even closer to one?

Thanks for pointing this out. Actually, the text was not clear. The scaling law for the lung's exchange surface $M^{11/12}$ is actually derived in West, Brown, Enquist 1997. This scaling is a direct consequence of their model that aims to explain why the metabolic rate scales as $M^{3/4}$ at BMR. Indeed, the fact that the exchange surface area scales almost as the body mass is surprising since the metabolic rate scales as $M^{3/4}$. This is actually due to the fact that the volume of the lung scales linearly with M , hence the exchange surface area, that represents most of the volume of the lung scales almost like it. We refer the reviewer to the paper of West et al. for more details about this derivation.

In our work, we use this scaling to show that the exchange surface area per unit of alveolar duct surface area ρ_S is independent on the mass. We made this clearer in the text.

In a more general way, we were more careful in citing the source or derivation of any allometric scaling laws in the paper.

In summary, I think this is a very interesting study. Making the paper more accessible to the general audience, which does not have the time to follow in depth every mathematical detail, but wishes to grasp the underlying logic of the arguments, would considerably increase the impact and could stress stronger the importance of the study.

Many parts of the paper were rewritten, we hope that it will be now far clearer and easier to read for a large audience.

Reviewer 2

Allometry is an important concept in biophysics. In the present paper, allometric relationships for lung ventilation in mammals are derived. I have not checked all the formulae. The ones I checked appear to be correct, except for the equation for $P_V(U,T)$, see my point (6) below. Overall, this is an interesting and valuable paper. I do have the following comments.

(1) Usually, allometric relationships are derived on the basis of approximations, sometimes very rough ones. For example, it is usually assumed that heat production is proportional to the 3rd power of body height/length. In the present paper, several rough approximations from the literature are used, for example, R to be proportional to $M^{(-3/4)}$. On the other hand, quite detailed equations are derived by the authors. While this can be appreciated, the question arises whether it is really necessary to indicate all coefficients or whether just proportionalities are needed.

Thanks a lot to raise this interesting point. The inclusion of the coefficients in our predictions shows that they give also good quantitative agreement with the physiology. We think this is an important point to show that the phenomena accounted for in our model predicts correctly the order of magnitude of the physiological quantities.

We understand that the allometric scaling of such quantities as R or C are rough, but nevertheless the laws predict correct order of magnitude. And so are our predictions. The indication of the coefficient for the input laws has another interesting benefit: it allows to reproduce our study and results.

We made this clearer in the text in the “results” section (page 6 before table II):

“Our model predicts exponents that are in accordance with the values observed in the literature, see Table II. Moreover, the predicted prefactors shows that our model is able to give quantitative predictions in accordance with the physiology.”

Also, we added the *table II* that focus on the predicted/observed exponents.

(2) Title: “lung's ventilation” better “lung ventilation”.

Corrected.

(3) p.1, l.h.s. "ATP is produced through a long and intricate chain of biochemical reactions". The authors probably have in mind the pathway of cell respiration. However, many cells, even in mammals, produce ATP partly by a highly active glycolysis with only little contribution by the TCA cycle and respiratory chain. Examples are the skeletal muscle, stem cells, endothelial cells and activated macrophages. Note that glycolysis only comprises 12 or 13 reactions (depending on the end product).

Thank you for this remark, indeed our explanation was not precise enough. As this is somewhat out of the scope of the paper, we chose to reduce this part of the introduction. We replaced this paragraph with:

"In animals, the cellular respiration is based on the aerobic oxidation of fatty acids and glucose that represents one of the major source of energy production [1]. Oxidative processes require oxygen to be brought from the atmosphere to each individual cell. In parallel, carbon dioxide, a major by-product of the cellular respiration, has to be removed from the tissues [2]. The capture and transport of oxygen and carbon dioxide is the role of the lung and of the blood network. The lung carries oxygen from the ambient air to its exchange surface with the blood network, which carries oxygen from the lung's exchange surface to the cells. Carbon dioxide is transported in the same way, but from the cells to the ambient air."

(4) p.1, l.h.s. "This energy conversion occurs mainly through oxidative processes". The same comment as in (1) applies. For the message of the paper, it is not so important, though, whether respiration is the main process of energy production or just one important process. Overall it is likely to be the main process due to the high molar ATP yield of respiration. If the authors want to maintain that, they should justify it and/or give references.

As for the previous point (3), we reduced this to the minimum as it is out of the scope the paper. We added the reference [1] = *H. Lodish, J. Darnell, A. Berk, P. Matsudaira, C. A. Kaiser, M. Krieger, M. P. Scott, and L. Zipursky, Molecular Cell Biology. W. H. Freeman, fifth edition ed., 2008.*

(5) It would be helpful for readers and reviewers to number all equations. In the present version, only some of them are numbered. This would also facilitate to cite equations within the paper, when new ones are derived.

Indeed, all the main equations are now numbered.

(6) p.2, r.h.s.: The equation for $P_V(U,T)$ should be explained better. To my eyes, neither the sentence before nor that after it explain it fully. The integral is taken over time. Shouldn't it then read "dt" at the end of the middle term?

Notice that we reorganized the text so that it becomes easier to read as suggested by the reviewer 1, so we removed most of the intermediate calculations that were breaking the text reading and put them as citations using the revtex footnote organization.

Thank you for pointing out the fact that the derivation of the elastic power was unclear. About P_V , we reformulate how to derive it fully in citation [21]. Similarly, we also gave more details on how we derive P_e in citation [20].

There was a misprint and “dt” was missing, thanks a lot for pointing this out.

(7) In the subsequent equation, the integral is taken over ds , and the upper bound is a point in time. Does s denote time here? That is defined only later, below eq. (3). Moreover, to explain that equation, it would help to mention that $u_0(t)$ is a sine function. If equations were numbered, the first one for $u_0(t)$ could be cited.

Again, we are sorry for the misunderstanding that comes from a misprint in the equation. Here dt should be used instead of ds . We renamed some of the mute variables in integrals so that no more confusion could occur with s , which is used later on as an dimensionless time.

(8) Top of p.3, l.h.s.: Has the symbol M been defined before using it? As far as I can see, it is defined only at the end of that subsection.

The mass M was actually defined very (too) early in the text, in the introduction (page 2, l.h.s, near the middle). We recalled the definition of M at the location of the text you are pointing out.

(9) p.4, l.h.s. “From [46], $r_0 = aM^{3/8}$.” Odd syntax. Better: “The allometric relationship between r_0 and M can be written as $r_0 = aM^{3/8}$ [46].”

Thanks a lot, we reformulated so the syntax is now proper.

(10) At some places, it would stylistically be better to drop the article “the”. For example: “the adenosine triphosphate”, “the carbon dioxide”, “the metabolism activity” (anyway perhaps better: “metabolic activity”).

We ran through the manuscript and check carefully the use of “the”. We corrected metabolism activity to metabolic activity.

Minor comments

(i) Why is airflow velocity denoted by $u_0(t)$ rather than just by $u(t)$? The subscript 0 suggests that it is the initial velocity.

The index 0 was the generation index 0. But indeed, this was not obvious in the text, so we removed the index from the main text.

(ii) p.2, r.h.s. “The parameterization using $(U; T)$ or $(VT; fb)$ are equivalent”: the noun should be in plural as well: parameterizations. Or stylistically better “The parameterization is equivalent for $(U; T)$ and $(VT; fb)$ ”

Corrected, thank you.

(iii) p.2, r.h.s. “These properties depends” should read “...depend”

Corrected.

(iv) p.2, r.h.s.: “Airflow velocity can be idealized by a sinusoidal pattern in time, i.e. under the form $u_0(t) = U \sin(2\pi t/T)$.” The given function is a (perfect) sine function, rather than a sinusoidal one. As the authors speak about idealization, they can immediately call it a sine-function pattern.

(v) p.3, l.h.s.: “Mammal’s lung shares” better “Mammalian lungs share“

Corrected.

(vi) p.3, l.h.s.: “auto-similar”. In the English scientific literature, the term “self-similar” is more common. Same in the legend to Fig. 1.

Corrected.

(vii) Legend to Fig. 1: “The conductive zone (beige) mimics the bronchial tree” sounds somewhat strange. I suggest writing “The bronchial tree is a conductive zone”. Analogously with “The respiratory zone (blue) mimics the acini”.

This is indeed not clear, thank you for pointing this out. We reformulated a bit differently:

“The tree in beige mimics the bronchial tree, where oxygen is only transported along the branches. The tree in blue mimics the acini, where oxygen is transported along the branches and also captured in the alveoli that cover the walls of the branches.”

(viii) p.3, r.h.s.: “As air is assumed incompressible in the lung in normal ventilation conditions [8]”. This is a counter-intuitive assumption. Can it be briefly explained rather than just by giving a Reference?

(ix) p.4, l.h.s.: “bronchi diameters” better “bronchial diameters”.

Corrected.

(x) p.5, r.h.s. “with VD the dead volume” better “with VD being the dead volume”.

Corrected.