Peer Community In
Mathematical & Computational Biology

How mammals adapt their breath to body activity – and how this depends on body size

Wolfram Liebermeister *based on peer reviews by* ***Stefan Schuster***, ***Oliver Ebenhöh***, ***Megumi Inoue*** *and* ***Elad Noor***

Frédérique Noël, Cyril Karamaoun, Jerome A. Dempsey, Benjamin Mauroy (2021) The origin of the allometric scaling of lung ventilation in mammals. arXiv, ver. 6, peer-reviewed and recommended by Peer Community in Mathematical and Computational Biology.
https://doi.org/10.48550/arXiv.2005.12362

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Published: 07 September 2021

How fast and how deep do animals breathe, and how does this depend on how active they are? To answer this question, one needs to dig deeply into how breathing works and what biophysical processes it involves. And one needs to think about body size.

It is impressive how nature adapts the same body plan – e.g. the skeletal structure of mammals – to various shapes and sizes. From mice to whales, also the functioning of most organs remains the same; they are just differently scaled. Scaling does not just mean "making bigger or smaller". As already noted by Galilei, body shapes change as they are adapted to body dimensions, and the same holds for physiological variables. Many such variables, for instance, heartbeat rates, follow scaling laws of the form y~x^a, where x denotes body mass and the exponent a is typically a multiple of ¼ [1]. These unusual exponents – instead of multiples of ⅓, which would be expected from simple geometrical scaling – are why these laws are called "allometric". Kleiber's law for metabolic rates, with a scaling exponent of ¾, is a classic example [2]. As shown by G. West, allometric laws can be explained through a few simple steps [1]. In his models, he focused on network-like organs such as the vascular system and assumed that these systems show a self-similar structure, with a fixed minimal unit (for instance, capillaries) but varying numbers of hierarchy levels depending on body size. To determine the flow through such networks, he employed biophysical models and optimality principles (for instance, assuming that oxygen must be transported at a minimal mechanical effort), and showed that the solutions – and the physiological variables – respect the known scaling relations.

The paper "The origin of the allometric scaling of lung ventilation in mammals" by Noël et al. [3], applies this thinking to the depth and rate of breathing in mammals. Scaling laws describing breathing in resting animals have been known since the 1950s [4], with exponents of 1 (for tidal volume) and -¼ (for breathing frequency). Equipped with a detailed biophysical model, Noël et al. revisit this question, extending these laws to other metabolic regimes. Their starting point is a model of the human lung, developed previously by two of the authors [5], which assumes that we meet our oxygen demand with minimal lung movements. To state this as an optimization problem, the model combines two submodels: a mechanical model describing the energetic effort of ventilation and a highly detailed model of convection and diffusion in self-similar lung geometries. Breathing depths and rates are computed by numerical optimization, and to obtain results for mammals of any size many of the model parameters are described by known scaling laws. As expected, the depth of breathing (measured by tidal volume) scales almost proportionally with body mass and increases with metabolic demand, while the breathing rate decreases with body mass, with an exponent of about -¼. However, the laws for the breathing rate hold only for basal activity; at higher metabolic rates, which are modeled here for the first time, the exponent deviates strongly from this value, in line with empirical data.

Why is this paper important? The authors present a highly complex model of lung physiology that integrates a wide range of biophysical details and passes a difficult test: the successful prediction of unexplained scaling exponents. These scaling relations may help us transfer insights from animal models to humans and in reverse: data for breathing during exercise, which are easy to measure in humans, can be extrapolated to other species. Aside from the scaling laws, the model also reveals physiological mechanisms. In the larger lung branches, oxygen is transported mainly by air movement (convection), while in smaller branches air flow is slow and oxygen moves by diffusion. The transition between these regimes can occur at different depths in the lung: as the authors state, "the localization of this transition determines how ventilation should be controlled to minimize its energetic cost at any metabolic regime". In the model, the optimal location for the transition depends on oxygen demand [5, 6]: the transition occurs deeper in the lung in exercise regimes than at rest, allowing for more oxygen to be taken up. However, the effects of this shift depend on body size: while small mammals generally use the entire exchange surface of their lungs, large mammals keep a reserve for higher activities, which becomes accessible as their transition zone moves at high metabolic rates. Hence, scaling can entail qualitative differences between species!

Altogether, the paper shows how the dynamics of ventilation depend on lung morphology. But this may also play out in the other direction: if energy-efficient ventilation depends on body activity, and therefore on ecological niches, a niche may put evolutionary pressures on lung geometry. Hence, by understanding how deep and fast animals breathe, we may also learn about how behavior, physiology, and anatomy co-evolve.

References:

[1] West GB, Brown JH, Enquist BJ (1997) A General Model for the Origin of Allometric Scaling Laws in Biology. Science 276 (5309), 122–126. https://doi.org/10.1126/science.276.5309.122

[2] Kleiber M (1947) Body size and metabolic rate. Physiological Reviews, 27, 511–541. https://doi.org/10.1152/physrev.1947.27.4.511

[3] Noël F., Karamaoun C., Dempsey J. A. and Mauroy B. (2021) The origin of the allometric scaling of lung's ventilation in mammals. arXiv, 2005.12362, ver. 6 peer-reviewed and recommended by Peer community in Mathematical and Computational Biology. https://arxiv.org/abs/2005.12362

[4] Otis AB, Fenn WO, Rahn H (1950) Mechanics of Breathing in Man. Journal of Applied Physiology, 2, 592–607. https://doi.org/10.1152/jappl.1950.2.11.592

[5] Noël F, Mauroy B (2019) Interplay Between Optimal Ventilation and Gas Transport in a Model of the Human Lung. Frontiers in Physiology, 10, 488. https://doi.org/10.3389/fphys.2019.00488

[6] Sapoval B, Filoche M, Weibel ER (2002) Smaller is better—but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proceedings of the National Academy of Sciences, 99, 10411–10416. https://doi.org/10.1073/pnas.122352499

Reviews

Evaluation round #3

DOI or URL of the preprint: https://arxiv.org/abs/2005.12362
Version of the preprint: 5

Authors' reply, 03 September 2021

Dear Wolfram,

Thanks a lot for your help. Here is the last version, which was also uploaded on arxiv as v6. Arxiv told me "Your replacement is scheduled to be announced at Mon, 6 Sep 2021 00:00:00 GMT."

Best,

Benjamin.

Download tracked changes file

Decision by Wolfram Liebermeister, posted 09 August 2021

Data availability and language editing

Dear authors,

As you can see, our reviewers have approved your preprint, and it is almost ready for recommendation. However, some things remain to be done. For a PCI recommendation, you need to comply with the following rules (which I hope you received in previous emails):

1) Data must be available to readers after recommendation, either in the text or through an open data repository such as Zenodo (free), Dryad (to pay) or some other institutional repository. Data must be reusable, thus metadata or accompanying text must carefully describe the data;

2) Details on quantitative analyses (e.g., data treatment and statistical scripts in R, bioinformatic pipeline scripts, etc.) and details concerning simulations (scripts, codes) must be available to readers in the text, as appendices, or through an open data repository, such as Zenodo, Dryad or some other institutional repository. The scripts or codes must be carefully described so that they can be reused;

3) Details on experimental procedures must be available to readers in the text or as appendices;

4) Authors must have no financial conflict of interest relating to the article. The article must contain a "Conflict of interest disclosure" paragraph before the reference section containing this sentence: "The authors of this article declare that they have no financial conflict of interest with the content of this article.";

5) This disclosure has to be completed by a sentence indicating that some of the authors are PCI recommenders: "XY is one of the PCI Math Comp Biol recommenders."

I think that rule 1 is satisfied (data are given in the text) and rule 3 does not apply. However, scripts or code (2) have neither been provided nor described. Please provide a usable version of your code with a brief description in some public repository such as Zenodo, Dryad or some other institutional repository (see Directory of Open Access Repositories) with a DOI. For rules 4 and 5, please add the required statements to the text.

Another point (which I had raised previously, and which has not been fully addressed): the language of your article is sometimes not idiomatic, and there are minor grammatical mistakes. Please have the manuscript thoroughly checked by a native speaker.

Details:

o In table 1, with r_A a minus sign seems to be wrong
o Appendix B 5: please specify the unit of a.
o As noted by one of the reviewers, there is one remaining question mark on page 3 after the sentence: "Moreover, some mammals species have specific branching pattern [40?]"

Reviewed by Elad Noor, 05 July 2021

The manuscript is now clearly written and it seems that the authors have addressed all my previous comments. I have no further remarks.

Reviewed by Megumi Inoue, 03 August 2021

The authors have made significant revisions and addressed my and other reviewers' concerns well in this edition. I appreciate the full explanation given by authors in addressing the core properties of branching patterns in mammalian lungs and its implications for the model. The additional data added, in accordance to physiological parameters found in literature, makes the model all the more persuasive. I noticed there is one remaining questions mark in page 3 after the sentence: "Moreover, some mammals species have specific branching pattern [40?]" Otherwise, I would like to recommend this edition for publication!

Evaluation round #2

DOI or URL of the preprint: https://arxiv.org/abs/2005.12362
Version of the preprint: 4

Authors' reply, 30 June 2021

Download author's reply
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Decision by Wolfram Liebermeister, posted 27 April 2021

Minor changes required

Dear authors,

You put a lot of work into this revision, and I think it was worth the effort!

Since the previous reviewers were not available for the second round of reviews, we recruited two new reviewers. As you can see from their comments, both of them are very happy with your manuscript. Please address their questions and suggestions for improvement.

Also, please make sure you comply with the following rule imposed by PCI Math Comp Biol:

-Details on the quantitative analyses (e.g., data treatment and statistical scripts in R, bioinformatic pipeline scripts, etc.) and details concerning simulations (scripts, codes) in the text, as appendices, or through an open data repository, such as Zenodo, Dryad or some other institutional repositories (see Directory of Open Access Repositories). The scripts or codes must be carefully described such that another researcher can run them.

I would like to add a few points from my side (which you can choose to address or ignore):

(1) Regarding the last point by reviewer 1 (what branching generations your model predicts), since you do not predict lung geometry directly, but use it to predict breathing volume and frequency, I would like to develop this question even further. Do you think that your results (breathing volume and frequency for basal, field, and maximum metabolic rates) may have a bearing, in reverse, on the ideal lung geometry (considering that in evolution, lung geometry and breathing patterns evolve together)? And, given that animals use their lungs in different "modes" (BMR, FMR or MMR), and that the relative importance of these modes may differ between species, do you think that one should differentiate between species (not just regarding body mass, but also regarding these different lifestyles) when predicting optimal lung geometry?

(2) At the end of "Ventilation pattern and energy cost of ventilation", it could be didactically good to explicitly state your optimality problem as a formula, something like

Maximize P(VT,fb) with respect to VT, fb subject to fO2(VT,fb,M) = fO2^demand(M,regime)

You could continue by saying that the two functions fO2(..) and fO2^demand(..) will be described next, that the optimization needs to be carried out numerically, and that the resulting optimal VT and fb, again, according to these calculations, show a scaling behavior.

(3) To justify Eq. (2), it seems that you argue that the lung tissue is fully elastic. Shouldn’t there also be extra energy loss because the tissue is not non perfectly elastic? Or is this a negligible effect?

(4) The way your simulation works is not fully clear to me. Do you simulate many rounds of inhaling and exhaling until all variables become periodic, and then determine the oxygen transfer? I’m asking this because I was wondering about your initial conditions for the oxygen partial pressure (and how much of an effect they have on the end result). And how do you run the numerical optimization?

(5) Your appendix VII is fantastic! Listing the main assumptions behind a model is a great service to the reader! Personally, I would suggest putting this appendix section first in the appendix because it provides a really good overview of the model.

I am looking forward to your new submission!

Best regards,

Wolfram

Reviewed by Elad Noor, 27 April 2021

Although I haven’t seen the original version of the manuscript, it seems that the text organization and clarity has significantly improved, and that all of the previous reviewers’ comments have been addressed. In addition, table 3 (the authors wrote in the reply that they added table 2, but I assume they meant 3) is indeed very helpful and clearly demonstrates that the approach is successful. Although I am not an expert on this topic, it seems very convincing that this model and the results are an important step in understanding the allometric scaling laws and filling in some of the existing gaps.

I only have a few minor comments:

- When the mass parameter (M) is introduced, add that it is always given in kg (this is important for the allometric scaling laws, where these units are not mentioned).
- I did find it a bit difficult to compare the fractions (predicted) to the decimal point values (observed) in table 1, e.g. when the predicted value was -1/12. Perhaps one could add a decimal value next to the fraction (in parentheses)?
- Placing footnotes among the reference list is new to me, and a bit uninuitive. I’m also curious if this wouldn’t break some of the automatic cross-referencing tools that exist in journals and aggregators. This is not a critical point, but I can suggest moving them to an appendix with multiple subsections (or a table with numbered bulletpoints), and keeping the citation list clean. Also, it should be clear if a reference is to a paper or to a footnote while reading the main text.
- There still remain quite a few grammatical errors, here is a partial list:
  - Page 3: ”see equation**s** 3” -> remove ”s”
  - Page 3: ”the depend**a**nce **to** the metabolic rate” -> ”the depend**e**nce **on** the metabolic rate”. The word ”dependence” is writted as ”depend<a>nce”, in at least one other occurance.
  - Page 6: ”This functional constrain **writes** in our model ...” -> I’m not sure what this means.
  - Page 6: ”corresponds to the mean need **in** oxygen of a mammal...” -> ”corresponds to the mean oxygen demand for a mammal of mass M”
  - Page 6: ”the approach is not able to predict the allomatric laws at other regimes than BMR” -> ”at regimes other than BMR”.

- Page 7: there is still a reference to "**the** carbon dioxide".
- Page 10: footnote 40 contains broken references - [?]

Reviewed by Megumi Inoue, 20 April 2021

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Evaluation round #1

DOI or URL of the preprint: https://arxiv.org/abs/2005.12362
Version of the preprint: 3

Authors' reply, 05 March 2021

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Decision by Wolfram Liebermeister, posted 16 November 2020

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. 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. 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. 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. 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? 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. ———- 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. (2) Title: "lung's ventilation" better "lung ventilation". (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). (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. (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. (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? (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. (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. (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]." (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"). 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. (ii) p.2, r.h.s. "The parameterization using (U; T) or (V_T ; f_b) are equivalent": the noun should be in plural as well: parameterizations. Or stylistically better "The parameterization is equivalent for (U; T) and (V_T ; f_b)" (iii) p.2, r.h.s. "These properties depends" should read "...depend" (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" (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. (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". (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". (x) p.5, r.h.s. "with VD the dead volume" better "with VD being the dead volume".

Reviewed by Oliver Ebenhöh, 28 October 2020

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.

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.

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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?

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.

Reviewed by Stefan Schuster, 16 November 2020

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. (2) Title: “lung’s ventilation” better “lung ventilation”. (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). (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. (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. (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? (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. (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. (9) p.4, l.h.s. “From [46], r0 = aM^3/8.” Odd syntax. Better: “The allometric relationship between r0 and M can be written as r0 = aM^3/8 [46].” (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”). 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. (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)” (iii) p.2, r.h.s. “These properties depends” should read “...depend” (iv) p.2, r.h.s.: “Airflow velocity can be idealized by a sinusoidal pattern in time, i.e. under the form u0(t) = U sin(2πt/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“ (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. (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”. (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”. (x) p.5, r.h.s. “with VD the dead volume” better “with VD being the dead volume”.