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Comments to the Author(s)/Editor(s)

Summary:

The authors propose a mathematical model for the growth of non-diffusive tumors based on energy conservation. The model takes into account the energy supply via the tumor microvasculature as well as the energy required for tumor maintenance and spatial expansion. The restricted energy supply leads to the well-known logistic growth law. Based on realistic parameter values found in the literature, the authors illustrate the impact of the various model parameters by means of simulations.

Major points:

1) **Page 2, Line 44:** The authors propose to illustrate their approach in the case of gliomas, suspectedly because numerical data were widely available. However, gliomas are highly infiltrative tumors, which invalidates the hypothesis of constant cell density among the tumor (Page 6, Line 8) and the biphasic approach adopted for the linear elastic model (Page 4, Lines 48-51). The more suited reaction-diffusion models have been extensively used for glioma growth modelling, see for example in [1-4].

   Whereas the aforementioned hypotheses may still hold for well-circumscribed (brain) tumors such as brain metastases, the numerical values used in the experiments may need to be adapted based on the literature. Or at least, if the order of magnitude of the parameters turned out to be similar, gliomas should not be mentioned as an example of application of this work.

   Also, it is not clear why the authors seek to apply this model exclusively to non-metastatic tumors on Page 6, Line 6. Brain metastases originating from other organs would on the contrary be more suited to the proposed model considering the remark hereabove.

2) **Page 4, Lines 14-15:** The creation of new vessels to maintain a constant microvascular density as the tumor growth also requires energy, which is expected to increase over time since the tumor volume is proportional to the exponentially increasing number of cells. This could explain the inconsistency highlighted at the end of Comment 4).

3) **Page 4, Line 51, Equation (4a):** The authors should provide a rationale for the linear dependency between E_p and E_s. The energy rate required for the tumor volume expansion should indeed depend on the external pressure but not on the supplied rate of energy.

Furthermore, the statement "It can be assumed that the change in volume of the normal brain tissue is directly proportional to the size of the tumor" on Lines 18-19 seems unsound. The correct statement would rather be that the infinitesimal decrease in volume of the normal brain is equal to the infinitesimal increase in the tumor volume as the whole brain volume can be considered constant due to the surrounding skull.

A more suitable approach would be to consider the tumor as a spherical solid under constant pression p due to the surrounding tissues. In first approximation, neglecting the tumor-induced change in the external pressure, the work required for an increase $\mathrm{d}V_T$ in the tumor volume would be [5]:

$$\mathrm{d}w = p\mathrm{d}V_T$$

Considering an incompressible tumor of cell density n_T, the energy rate is then given by:

$$E_p = \frac{\mathrm{d}w}{\mathrm{d}t} = p\frac{\mathrm{d}V_T}{\mathrm{d}t} = \frac{p}{n_T}\frac{\mathrm{d}N_T}{\mathrm{d}t}$$

With this approach, the energy required for tumor expansion is coupled to the growth rate and thus to the number of cells for an exponential or logistic growth.

Nevertheless, this approach remains simplistic. The mechanical effects of tumor growth have been more extensively studied in the literature, for example in [6, 7]. A suitable level of modelling should be adopted here to accurately capture the process involved while being able to derive an analytical expression that can be fed with realistic numerical parameter values.

4) **Page 6, Lines 13-17, Equation (6a):** The authors should provide a rationale for the linear dependency of the net growth rate in the fraction of energy available for the creation of new cells $\frac{E_g}{E_S}$.

More generally speaking, the problem of resource-dependent growth of cell populations has been extensively studied previously, for example in [8]. The main idea of these models is that the *residual energy* after subtraction of the energy required for cell maintenance can be used for growth, i.e. creation of new cells (and the compensation of the external pressure required for tumor expansion), rather than the energy ratio. In this respect, a quota-based model such as the one proposed by Droop [8, 9] may be more appropriate for the problem addressed by the authors.

This model states that cell can only divide if it accumulated a certain quota Q (e.g. energy or more exactly glucose molecules) of resource larger than the subsistence quota q (i.e. the minimum amount of resource required to maintain a cell). Based on experimental observations on algae, Droop proposed the following law (using the author's notation):

$$\frac{dN_T}{dt} = gN_T\left(1 - \frac{q}{Q}\right), \qquad \text{if } Q \geq q \text{ else } 0$$

where q is the cell subsistence quota, Q is the cell quota, and the other symbols are defined as in the manuscript.

The original work considered a closed system with fixed total amount of resource, but a fixed flux of resource can be considered as well, as suggested by the authors. Ignoring the effects of spatial expansion for which the modelling steps should be further justified (see Comment 2)), this would lead to:

$$\frac{dQ}{dt} = \frac{d}{dt}\left(\frac{\varepsilon_T}{N_T}\right) = \frac{E_s N_T - \varepsilon_T N_T g\left(1 - \frac{q}{Q}\right)}{{N_T}^2} = \frac{E_s}{N_T} - g(Q - q)$$

where $\varepsilon_T = Q N_T$ is the total energy of the system at time t (supposedly entirely captured by all N_T cells before being used for multiple purpose) and the other symbols are defined as in the manuscript.

Considering a quasi steady-state for the quota Q as in [8], we have:

$$Q = \frac{E_s + qgN_T}{gN_T}$$

And then:

$$\frac{dN_T}{dt} = gN_T\left(1 - \frac{qgN_T}{E_s + qgN_T}\right) = gN_T\left(1 - \frac{qgn_T}{\alpha_{sr}\alpha_{s0}A_{cs} + qgn_T}\right)$$

Note the strong similarity between the equation hereabove and Equation (6b) of the manuscript (ignoring the effects of space), in particular when defining $\alpha_r = qg$ (units W/cell). However, the additional term of the denominator of the equation derived herein solves a major issue of Equation (6b), that is the net proliferation of tumor cells tends to -∞ (i.e. instantaneous death of all cells) as $\alpha_{sr}\alpha_{s0}A_{cs}$ tends to 0 (i.e. the energy supply is stopped).

We see that, ignoring the effect of spatial expansion, the tumor has an exponential growth as long as the vasculature (and thus the energy supply) is proportional to the number of cells (see Equation (2d)), which is probably unrealistic. This issue may partly originate from the fact that creating new vessels also requires energy, which is not taken into account in the manuscript as pointed out in Comment 2).

5) **Page 6, Line 19:** For consistency with Equation (6a), g should not be seen as "the result of cell creation rate minus death rate" as stated by the authors. Indeed, if $\frac{E_g}{E_s}$ becomes 0, Equation (6a) suggests a constant number of cells over time whereas it is expected to decrease due to natural cell death at constant rate. Instead, an additional death term which does not depend on the energy available for growth should be added.

6) **Pages 10-15:** The presented results and discussion might change significantly considering the previous comments.

Minor points:

7) **Page 1, Line 16:** The formulation "creation of space" is confusing. "Tumor volume expansion" would be more appropriate. The same remark applies to Page 2, Line 35; Page 3, Lines 2, 25-26 and 42; Page 4, Line 48 and Page 14, Line 53.

8) **Page 1, Lines 21-38:** Parts of the results should be removed from the abstract as they make the main message unclear. On the other hand, the rederivation of the well-known logistic law, which seems to be a major finding of the study, may be mentioned.

9) **Page 2, Lines 16-17:** "Among these Logistic growth and Gompertzian growth models are suitable for the study of tumor growth" should be rephrased as it discards the other two model types mentioned just before without justification.

10) **Page 5, Lines 50-51:** For unit consistency, the units of α_n should be mm³/cell instead of mm³.

11) **Page 6, Lines 29-32, Equation (6b):** It could be interesting to rewrite the equation under its canonical form:

$$\frac{dN_T}{dt} = rN_T\left(1 - \frac{N_T}{C}\right)$$

with r being the *actual* maximum growth rate and C the carrying capacity.

By identification with Equation (6b), we have:

$$r = (1 - \alpha_n n_T)g$$
$$C = \frac{(1 - \alpha_n n_T)n_T}{\alpha_p K_v}$$

In this way, the influence of the various parameters introduced by the authors on the actual maximum growth rate and the carrying capacity could be further discussed, which could greatly benefit the discussion and the whole study.

12) **Page 6, Lines 40-44:** For consistency with Equation (1), it should be worth clarifying that $\frac{dN_T}{dt} = 0$ implies $E_g = 0$ and the unchanged volume implies $E_p = 0$, *hence* $E_r = E_s$.

13) **Page 6, Line 46-53:** "[…] $N_T(t) = 1$ to $N_T(t) = N_T$" should be "[…] $N_T(\mathbf{0}) = 1$ to $N_T(t) = N_T$".

Besides, for the sake of generality, it should be interesting to solve the equation for an arbitrary initial number of cells $N_T(0) = N_0$. Based on the well-known solution of the logistic equation and the derivation of the actual growth rate r and carrying capacity C made in Comment 11), we then have:

$$N_T = \frac{CN_0\mathrm{e}^{rt}}{C + N_0(\mathrm{e}^{rt} - 1)} = \frac{(1 - \alpha_n n_T)\boldsymbol{N_0}\mathrm{e}^{g(1-\alpha_n n_T)t}}{(1 - \alpha_n n_T) + \frac{\alpha_p K_v}{n_T}\boldsymbol{N_0}(\mathrm{e}^{g(1-\alpha_n n_T)t} - 1)}$$

14) **Page 7, Lines 10-18:** This result comes trivially after noticing that the carrying capacity C verifies:

$$C = \frac{(1 - \alpha_n n_T)n_T}{\alpha_p K_v}$$

which is by definition the maximum number of cells that the system can hold. A more in-depth analysis of the impact of the parameters based on the properties of the logistic function after identification of the growth rate r and carrying capacity C (see Comment 11)) should be conducted instead.

15) **Page 7, Line 38-42, Equation (9):** For the sake of generality, it could be interesting to derive the value for an arbitrary initial number of cells $N_T(0) = N_0$ based on the results in Comment 11), we have:

$$\frac{CN_0 e^{rt_{Tmax99}}}{C + N_0(e^{rt_{Tmax99}} - 1)} = 0.99C$$

$$\Leftrightarrow t_{Tmax99} = \frac{1}{r}\log\left(\frac{99(C - N_0)}{N_0}\right) = \frac{1}{g(1 - \alpha_n n_T)}\log\left(\frac{99\left(1 - \alpha_n n_T - \frac{\alpha_p K_v}{n_T}\boldsymbol{N_0}\right)n_T}{\alpha_p K_v \boldsymbol{N_0}}\right)$$

16) **Page 9, Lines 17-18:** As discussed in Comment 1), the example of gliomas may be unsuitable for the proposed model since these are highly infiltrative tumors with spatially variable cell density. The numerical values might be adjusted if other types of tumors are considered.

17) **Page 9, Lines 24-32:** This relation can also be found using the definition of the maximum growth rate r:

$$r = (1 - \alpha_n n_T)g \geq 0$$

The greater or equal inequality symbol should be more appropriate for consistency with Equation (10c)

18) **Page 10, Lines 23-40 and Table2:** The derived values of g seem a bit too large compared to the literature. Indeed, considering the net growth rate of the logistic function:

$$r = (1 - \alpha_n n_T)g$$

we have, for $\alpha_n = 4.687 \times 10^{-6}$mm^3, $n_T = 1.84 \times 10^5$mm^{-3}, and $g = 7.457 \times 10^{-5}$s^{-1}, $r = 323.56$yr^{-1}. The literature on glioma growth modeling rather suggests rates in range 1.70-50.29yr^{-1} [4, 10-13]. Some parameters used for the derivation of g may have been misestimated. After possible corrections, relating the derived value of r to the wide literature on glioma growth modeling (if the use of gliomas as an example can be motivated) could give more weight to the paper.

Using $g = 1$d^{-1} on Page 11 Lines 4-5 leads to $r = 50.22$yr^{-1}, which is more in accordance with the literature. But then, this choice of g should be motivated with regard to Table2.

Also, the value of g is higher in LG than in HG in Table2, which is inconsistent (see also Comment 30)).

19) **Pages 10-12:** Reminding the signification of the various symbols when they first appear would greatly facilitate the reading of the Results section.

20) **Page 11, Line 8:** "Variation of N_{TM} and t_{Tmax99} with three values of α_p is shown in Figure1(B)." should be changed to "Variation of N_{TM} and t_{Tmax99} **with $\boldsymbol{\alpha_n}$ for** three values of α_p is shown in Figure1(B)."

21) **Page 11, Lines 15-23:** These comments seem to be related to Figure1 (A) and should appear at Line 5 before presenting the results of Figure1 (B).

22) **Page 11, Lines 24-35:** These are well known results of logistic growth and in fact reflect the influence of the growth rate r and carrying capacity C on the tumor volume/population. Orienting the presentation of the results towards how the model parameters affect the global r and C would be more relevant since the reader could then be referred to the well-known properties of logistic laws.

23) **Page 12, Lines 8-13:** Again, these results come trivially when noticing that the carrying capacity $C = \frac{(1-\alpha_n n_T)n_T}{\alpha_p K_v} \sim n_T - {n_T}^2$ for the other parameters kept constant. The same remark holds for the influence of α_p.

24) **Page 12, Lines 24-25: "**The values of N_{TM} are decreased with the increase of α_n" should be **"**The values of N_{TM} are decreased with the increase of $\boldsymbol{\alpha_p}$".

25) **Page 12, Lines 26-34 and Figure3 (D):** Considering Equation (6b) for fixed values of α_n, n_T and α_p, varying $\frac{E_g}{E_s}_{t=0}$ is to vary K_v. Considering the definition of the carrying capacity $N_{TM} = \frac{(1-\alpha_n n_T)n_T}{\alpha_p K_v}$ and Equation (6b), I would have expected that $N_{TM} \sim \frac{1}{1-\frac{E_g}{E_s}_{t=0}}$. Could the authors comment?

26) **Pages 12-15:** A pragmatic reflection on how these results could be used to improve treatments and/or patient management could greatly benefit the discussion, especially for a journal in applied sciences. A few words and the limitations of the approach adopted should also be added, especially as several model design steps are not sufficiently motivated.

27) **Page 12, Lines 47-48:** With regard to Comment 4), a reasoning based on the residual (not fraction of) energy remaining to growth should be more appropriate.

28) **Page 13, Lines 37-41:** According to Equation (5a), the initial energy ratio would be rather:

$$\frac{E_g}{E_s}_{t=0} = 0.5 - \frac{\alpha_p K_v}{n_T}$$

since $N_T(0) = 1$ (Page 6, Line 46). Could the author comment?

29) **Page 14, Lines 33-35:** As pointed out in Comment 1), gliomas are highly infiltrative tumors with spatially varying cell density, hence the mean n_T is not very informative.

30) **Page 14, Lines 46-49:** "The intrinsic growth rate g resembles the mitotic rate, was found more in high grades than low grades for the same values of V_{TM}, α_p, and t_{Tmax99} as presented in Table5.": the opposite is shown in Table2, as pointed out in Comment 18).

31) **Page 15, Lines 12-25:** The paragraph would be more suited to the discussion section.

32) **Page 15, Lines 14-17:** The statement that the "larger variations in nuclear size, shape, and nuclear to cytoplasm" is a consequence of the cells not "giving much attention to its maintenance" should be supported by a reference as it does not seem obvious.

33) **Page 15, Line 18:** What do the authors mean by "a tumor could be trained"?

34) **Pages 21 and 23, Figures 1 and 3:** The units of the cell population (i.e. "(cells)") should be specified for more clarity.

35) **Page 19, Table3:** What is the meaning of "-ve"?

Conclusion:

The approach of coupling a classical exponential growth model to the restrictions of energy supply via the microvasculature and the energy requirements for spatial expansion via an elastic model is interesting, especially since these restrictions yields the well-known logistic law. Nevertheless, several modelling steps are not sufficiently justified and seem unsound. I would not recommend rejection beforehand since a valuable effort has been made to derive realistic parameter values and the subsequent analyses are of interest, though they should be further commented on a practical cancer management aspect. However, revisions and/or further justifications are required for the model equations, which may in turn change the results and conclusion of the present study.

References:

[1] Clatz, O. et al. Realistic Simulation of the 3-D Growth of Brain Tumors in MR Images Coupling Diffusion With Biomechanical Deformation. *IEEE Transactions on Medical Imaging* 24, 1334–1346 (2005).

[2] Swanson, K. R., Rostomily, R. C. & Alvord, E. C. A Mathematical Modelling Tool for Predicting Survival of Individual Patients Following Resection of Glioblastoma: A Proof of Principle. *British Journal of Cancer* 98, 113–119 (2008).

[3] Konukoglu, E., Clatz, O., Bondiau, P.-Y., Delingette, H. & Ayache, N. Extrapolating Glioma Invasion Margin in Brain Magnetic Resonance Images: Suggesting New Irradiation Margins. *Medical Image Analysis* 14, 111–125 (2010).

[4] Rockne, R. et al. Predicting Efficacy of Radiotherapy in Individual Glioblastoma Patients in Vivo: A Mathematical Modeling Approach. *Physics in medicine and biology* 55, 3271–3285 (2010).

[5] Lunati, I. Young's Law and the Effects of Interfacial Energy on the Pressure at the Solid-Fluid Interface. *Physics of Fluids* 19, 118105 (2007).

[6] Kalli, M. & Stylianopoulos, T. Defining the Role of Solid Stress and Matrix Stiffness in Cancer Cell Proliferation and Metastasis. *Front. Oncol.* 8, 55 (2018).

[7] Wasserman, R., Acharya, R., Sibata, C. & Shin, K. H. A Patient-Specific In Vivo Tumor Model. *Mathematical Biosciences* 136, 111–140 (1996).

[8] Kuang, Y., Nagy, J. D. & Eikenberry, S. E. Resource Competition and Cell Quota in Cancer Models. In *Introduction to Mathematical Oncology*. 196–225 (2015).

[9] Droop, M. R. Some Thoughts on Nutrient Limitation in Algae. *Journal of Phycology* 9, 264–272 (1973).

[10] Szeto, M. D. et al. Quantitative Metrics of Net Proliferation and Invasion Link Biological Aggressiveness Assessed by MRI with Hypoxia Assessed by FMISO-PET in Newly Diagnosed Glioblastomas. *Cancer Research* 69, 4502–4509 (2009).

[11] Rockne, R. C. et al. A Patient-Specific Computational Model of Hypoxia-Modulated Radiation Resistance in Glioblastoma Using 18F-FMISO-PET. *Journal of the Royal Society Interface* 12, (2015).

[12] Lipkova, J. et al. Personalized Radiotherapy Design for Glioblastoma: Integrating Mathematical Tumor Models, Multimodal Scans and Bayesian Inference. *IEEE Trans. Med. Imaging* 38, 1875–1884 (2019).

[13] Konukoglu, E. et al. Image Guided Personalization of Reaction-Diffusion Type Tumor Growth Models Using Modified Anisotropic Eikonal Equations. *IEEE Transactions on Medical Imaging* 29, 77–95 (2010).