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Review of “Accounting for the adaptation of cell membrane adhesion during the uptake of random nanoparticles”

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^E Editor

Authors Dear Editor and Reviewers, Thank you very much for your valuable suggestions and comments on our paper. Your insights have greatly contributed to enhancing the quality of this manuscript. We have thoughtfully incorporated revisions into our paper in line with the reviewer’s recommendations, and these changes are indicated in red within the manuscript. Please find below the comments from each reviewer and our corresponding answers. We sincerely hope that you find our responses and modifications satisfactory.

Review of version 1

Permalink: <https://hal.science/hal-04266009v1>

Reviewer 1 (Anonymous)

Reviewer The present paper discusses the relevance of adhesion energy in the cellular uptake of nanoparticles. The main contribution appears to be in the formulation (4) of the adhesion energy, which is made dependent upon the wrapping degree f . This statement appears to be reasonable, since numerical evidence show that the receptors may localize at the edge of the wrapped area, see for instance:

- M. Serpelloni, M. Arricca, C. Ravelli, E. Grillo, S. Mitola, A. Salvadori (2023), Mechanobiology of the relocation of proteins in advecting cells: modeling, experiments, and simulations, *Biomechanics and Modeling in Mechanobiology*, 22:1267–1287 <https://doi.org/10.1007/s10237-023-01717-2>
- Serpelloni, M. Arricca, M.; Bonanno, C.; Salvadori, A.; Chemo-transport-mechanics in advecting membranes. *International Journal of Engineering Science*, Volume 181, 1 December 2022, 103746. <https://doi.org/10.1016/j.ijengsci.2022.103746>

Most of the paper content is devoted to a sensitivity analysis of Eq (4), either for spherical or elliptical particles. I believe the paper is sound and deserves publication. I would recommend to:

Clarify better the form of Eq (4), relating it to the physical evidences in receptors-ligands interactions.

Authors To further clarify the physical meanings of the parameters that we used in our three-parameter sigmoid evolution model, introduced in Eq (4), in the new version of the paper, we have added a sentence in the paragraph right after this equation (about three lines after the beginning of the paragraph).

Reviewer Compare outcomes with constant and wrapping dependent adhesion energies, to estimate the real impact of the latter.

Authors To illustrate the effect of the mechano-adaptation, in the new version, we have added figure 7b to

compare the variation of the phase proportions in terms of the NP's aspect ratio, depending on whether the membrane exhibit a passive or mechano-adaptive behavior.

Reviewer Modify figure 2, which seems not to correspond to the text at the end of section 2.

Authors Figure 2 has been modified according to this comment, ensuring that both sides of the free membrane touch, for illustration of the phase 3.

Reviewer 2 (Anonymous)

Reviewer This paper extends a previous model to reproduce the evolution of the adhesion between nanoparticles (NPs) and membrane cells during the uptake of drug nanoparticles in cells. For that, the authors proposed a sigmoid function formulated in terms of three main variables, namely: the amplitude and the delay of the transition, and the curvature parameter. With this approach, adhesion is not constant anymore. A sensitivity analysis is performed to study the influence of each parameter on the outputs of the models using a Kriging surrogate modeling. Then the geometric influence is studied by considering different elliptic shapes with different aspect ratios (including the one for the circumference).

Reviewer The title and part of the abstract may be confused or too general when the authors mention the mechanical response or mechanical properties of the cell membrane. The authors consider only (if I am not mistaken) adhesion as the only mechanical property. Moreover, in the abstract, the authors start mentioning in the description of the problem "the NP's mechanical and geometrical properties". Then, with no transition, the authors start the "Reason for writing" part mentioning the importance of the adhesion. This should be clarified.

Authors According to this comment, we changed the title of the paper to: "Accounting for the adaptation of cell membrane adhesion during the uptake of random nanoparticles" to put the emphasis on adhesion. Subsequently, changes have also been made in the abstract (phrase starting at the third line of the first paragraph), the keywords (adhesion added), and the introduction (the last phrase before the second paragraph).

Reviewer There are many parameters and some of them are defined after appearing in the text for the first time. A table with the parameters and their definition would help the reading.

Authors In the new version of the paper, a nomenclature has been added to the end of the article (see Section 9) that summarizes the parameters along with the abbreviations used within the text. A reference to this nomenclature has been added at the end of the paragraph right after Eq (1).

Reviewer I think that there is room to improve the introduction. For example:

Reviewer I presume that the uptake of nanoparticles involves different phases and that the authors studied only the wrapping. If it is so, the complete description of these phases should be included remarking the importance of the wrapping.

Authors Indeed the uptake of NPs occurs in different phases and our main focus in this paper is on wrapping. As suggested by the reviewer, we modified the introduction to provide more details on the steps of the internalization of NPs. The corresponding modifications can be found from the 10th line of the first paragraph of the introduction onwards. Another small modification has also been added to the line 13 of the page 2 to insist that the main focus of the paper is on wrapping.

Reviewer A description of the mechanical processes involved in the uptake of NPs should be included, justifying why adhesion is a relevant issue. Probably, most of section 3.1 should be detailed and enlarged in the introduction.

Authors The mechanical processes involved in the wrapping process have been added to the Introduction, first paragraph, from the line 11 up to 15.

Reviewer The authors mention "The main approaches are commonly used according to the scale at which the problem is investigated." What those approaches are? A summary of how the uptake is modeled a different scales should be included.

Authors This point has been addressed by adding some details to the introduction. In particular, we

mentioned molecular dynamics-based approaches and the ones at the scale of the nanoparticle. This has been added in a sentence starting at the line 15 of the introduction’s first paragraph.

- Reviewer** In the same way, when the authors state “Models at the scale of the NP have mostly been developed by Yi, Shi, et al. (2011) and were already present in our previous article in a stochastic framework (Iaquinta et al. 2022)”, they should comment that these are the unique approaches at NPs scale or show how other formulations have modeled this issue.
- Authors** This question has been addressed in our answer to the previous question (see c above).
- Reviewer** The title of the Section 2 should be changed. An idea could be to create a new Section 2 with a title relative to the mechanical modeling of the adhesion and two subsections: 2.1 Previous proposal, 2.2 New proposal (it is just an idea, I let the authors the final decision).
- Authors** We appreciate the reviewer’s suggestion regarding the title and structure of Section 2. However, after careful consideration, we believe that changing the title/structure of this Section may not necessarily enhance the coherence and readability of the paper. The primary objective of Section 3 is to present the phenomena occurring within the membrane in order to highlight that the tension $\bar{\sigma}$ should be kept constant and by contrast, the adhesion $\bar{\gamma}$ varies during the wrapping process. We have added an additional sentence to the end of the Section 3.1.2 to clarify this point.
- Reviewer** In Section 3.1, it is not clear the difference between specific and non-specific adhesion. In the case of the study, which one of them is given? Do the membrane receptors play the same role in both types of adhesion?
- Authors** The difference between the specific and non-specific adhesions is that the former is due to receptor-ligand bonds, while the latter is for instance due to van der Waals interactions. However, we believe that a discussion about the difference between specific and non-specific adhesions does not help the understanding of the reader and should thus be removed. Changes have been made in this regard at the beginning of Section 3.1.2.
- Reviewer** In the introduction, the authors state that “Cancer cells are for instance less stiff compared to their healthy counterparts (Lekka et al. 2012; Lin et al. 2015; Hall 2009; Suresh 2007). In addition, they also adhere less to the extra-cellular medium (Yang et al. 2013; Haley et al. 2008; Kuo et al. 2018; Kanyo et al. 2020). It could therefore be theoretically possible to control the uptake of NPs by cells of different types based on a mechanical differentiation.” In the abstract, they also state that “the objective is to optimize the NP’s mechanical and geometrical properties to enhance their entry into cancer cells while avoiding benign ones.” However, this objective has not been modeled. If it is not an objective, the sentence of the abstract should be deleted.
- Authors** Indeed, the mechanical targeting of anti-cancer nanovectors is the main context of our research and the topic of this article is solely a contribution to this goal. The corresponding modifications can be found in the third line of the abstract, and the end of the introduction’s first paragraph.
- Reviewer** Section 4.1.1 should be explained more in detail. For example, how is $\psi/3$ obtained? Is it related to energy? If it is so, it should be explained. How many NPs are considered to obtain it? How is the phase diagram obtained?
- Authors** In the new version, figure 6 has been added to more clearly explain the steps to be followed in order to calculate the phase proportions Φ_i for a given set of input parameters $(\bar{\gamma}_A, \bar{\gamma}_D, \bar{\gamma}_S, \bar{s})$. The steps are as follows: (1) for each tuple $(\bar{\gamma}_0, \bar{\sigma})$, taken within the domain of definition of the variables, the variation of dimensionless energy $\bar{\Delta E}$ in terms of the wrapping degree f is computed to identify the equilibrium position and thus (2) the equilibrium phase, that is used to (3) build the phase diagram wherein each color corresponds to an equilibrium phase i . Finally, (4) the phase proportions Φ_i are computed as the ratio of tuples $(\bar{\gamma}_0, \bar{\sigma})$, that yield the phase i divided by the total number of tuples. This number of tuples was set after a convergence study on Φ_i to 280. In the revised version of the article, these details are added to Section 4.1.1.
- Reviewer** A figure that represents the flux of calculation would help to understand the equations shown in the paper and subsections 4.1.1 and 4.1.2.

Authors This question has been addressed in our answer to the question 7 (see above).

Editor's assessments (Anna PANDOLFI)

This article extends an existing model to mimic the adhesion between nanoparticles and membrane cells during the uptake of drugs. The reviewers find the work sufficiently original because of the description of the evolution in time of the adhesion model and the accurate sensitivity analysis performed.

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