TO: Alan Schwartz <originseditor@outlook.com>

Dear Dr. Schwartz:

Thank you very much for your email. Please, find below detailed description of corrections. My responses are marked as KK. In order to avoid confusion, I am referring below using manuscript page numbers (which are in the bottom right corner of each page), not PDF page number.

Best regards,

Konstantin Konstantinov

**About the reported work**

• This work is about the simulations of kinetic models of chemical systems that are fed from achiral compounds, that can synthesize chiral monomers (possibly catalyzed by a specific polymer), their polymerization (possibly requiring an activation step), epimerization of some polymers, and the sedimentation of a specific pair of polymers.

• The authors investigate the possibility to obtain *robust* deracemisation towards different catalytic rates (i.e. the possibility to obtain symmetry breaking without the necessity of fine tuning the system parameters).

• This is performed by the study of the stability of the racemic state Globally, this work is based on classical models of deracemization as studied in the literature, focusing on polymerization/depolymerization of amino acids. Essentially, the novelty of this work is to give some clues on the possibility for some specific peptide sequence possessing some specific

**Major comments**

*• The corrections from the previous article seems to have been correctly taken into account. The calculations now seem to be correct.*

**KK: Ok.**

*• Considering the notion of "closure" as used by the author (it consists in irreversibly and instantaneously activating "waste compounds" back into "food" compounds), it must be realized that it always implies a continuous chemical energy input into the system (there is an input of chemical energy from the activation reaction from wastes to food, that comes down to the energy exchange link to the matter exchange in its "open-flow" equivalent).*

**KK: Clarification that closure requires inflow of energy was added. See page [REF].**

*• The authors must realize that this "closure", characterized by the recycled sedimentation process (P1+P2 \_nY, followed by Y\_A) is strictly equivalent to an implicit activation process (i.e. the formation of A\*) due to irreversible nature of the sedimentation process (it necessarily implies the input of chemical energy). Actually, no symmetry breaking process would be thermodynamically possible without chemical activation (in such a case, the absence of chemical input will doom the system to its thermodynamic equilibrium, and thus to a racemic state). The simulations in presence or 1 absence of explicit activation are thus essentially equivalent (all systems actually contain an implicit activation process).*

**KK: .**

*• The results essentially show that there is symmetry breaking in extended Frank systems (catalyzed formation of chiral compounds, and elimination of pairs of compounds), taking into account an intermediate polymerization. The symmetry breaking is thermodynamically feasible thanks to being in a far from equilibrium state, due to the activation of sedimenting peptides back to food compounds Y (or its equivalent of a continuous energy input via a continuous feeding of Y in the open-flow version), and thanks to efficient catalysis and/or elimination of some peptide pairs. The major new and potentially interesting result is the fact that this symmetry breaking only occurs with specific pairs of sedimenting polymers. However, this point is only observed, and not even discussed. Why these specific pairs? This is the interesting point.*

**KK: DISCUSS.**

*• The authors concludes that the cycled sedimenting models are more robust than APED model, because the latter one relies on the fine tuning of some kinetic parameters. . . but they omit the fact that sedimenting models also relies on another fine tuning: the precise choice of the sedimenting pairs! This lack of robustness is actually observed and described by the authors: it is sufficient to slightly extend the model by an additional sedimentations (i.e. both Eq. 28 and 29) for decreasing the robustness (the system then requires a fine tuning of the window of concentrations, as stated in page 36, then 38).*

**KK: There is a crucial difference between fine tuning of some chemical coefficients and adjusting the concentrations. The coefficients are what they are and as such they cannot be changed. Requiring that they have some particular values for the model to operate is fine-tuning. The concentrations, on the other side, can be easily adjusted by adding or removing solvent and, therefore, there is no fine-tuning in such models. For example, a standard attrition-enhanced deracemization (Viedma ripening) also has some constraints on concentrations: if we add too much solvent, then there will be no sediment at all and attrition-enhanced deracemization will not work. We added relevant clarifications. See, page [REF].**

**Minor points**

*• in page 6, the authors are writing that "surprisingly, the total enantioselectivity was ’allowed’ to deviate from [. . . ] 0"; criticizing the fact that many authors have considered that possibility (that comes down to assume some fundamental asymmetry, typically assuming the possibility of weak forces fundamental asymmetry to influence chemical reactions). . . but then, the author are making the very same assumption (p30, "Symmetry breaking in the presence of weakly enantioselective catalytic synthesis")*

**KK: We are not making the same assumptions. To clarify, we changed the paragraph name to "** **Symmetry breaking in the presence of weakly enantioselective forward catalytic synthesis " and adjusted some text in that paragraph. See, page [REF].**

*• The 3D figures (Fig 2-17) are really a bad choice, and rendering them bigger is not a solution. They are very difficult to read: the information they contain comes down to identify which pair of peptide can give rise to a 2 symmetry breaking, that is to identify to which line/column belongs each 3D- bar in each graphic. The only way I had o be able these graphics was to print and use a pen and ruler to correctly get these informations. A simple matrix of data would be far more easy to read, would take less place, while containing the very same information! Moreover there are far too many figures in this article. Please only select the most characteristic ones, and include the other one as supplementary material.*

**KK: Our first version of the article (which we have not submitted) actually had tables. However, we abandoned the idea because 62x62 tables are also very difficult to work with. Rather, we wanted to illustrate the difference among all possible combinations and that resulted in the submitted pictures. In the current version we put the most important information into tables (thus making them much smaller than 62x62) and left only a few pictures for those who prefer pictures over tables.**

*• The article is still very difficult to read, as there are many notations, symbols and parameters, and are defined throughout the text, so that one as to go a lot back and forth the text for understanding the details. The article would gain clarity summing up all these notations.*

**KK: We are not sure that we can address that point. The notations and parameters are introduced and then discussed as they occur in the text. The number of parameters and notations is large because the models that we considered are complicated. Putting all notations and parameters into a separate paragraph would still require cross referencing that paragraph for any clarifications. In addition, it will also separate the definitions from discussions and that might make the understanding of the text even more difficult.**

**Conclusion**

*This article is globally correct, with some interesting results, and its scientific content is sufficient for being considered for publication; however:*

*1. the article id badly organized: a profusion of notations dispersed within the text, and a bad choice and too large number of figures*

**KK: The number of figures has been substantially reduced and the most important information is now reported in several small tables. The number of parameters and notations cannot be decreased without sacrificing the discussion and we prefer to introduce parameters and notations as they occur rather than to summarize them into a single paragraph.**

*2. it consists more in observations than explanations; some interesting finding seems to have ben uncovered (namely the possibility of symmetry breaking only when some specific pairs of peptides are allowed to sediment), but they are barely discussed.*

**KK: .**

*As a consequences, I think that this work can be published, once the article*

*would have been revised taking into account these two major points.*

**KK: .**